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(54) **LIR-9, A NOVEL LEUKOCYTE
IMMUNOGLOBULIN-LIKE RECEPTOR**

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(57) **ABSTRACT**

A new family of immunoreceptor molecules of the immuno-
globulin superfamily, (LIR) polypeptides is described. Dis-
closed are sequences encoding LIR family members and their
deduced amino acid sequences, polypeptides encoded by
DNA that hybridizes to defined nucleotide sequences, pro-
cesses for producing polypeptides of the LIR family, and
specific antibodies directed against LIR polypeptides. LIR
family members can be used to treat autoimmune diseases
and disease states associated with suppressed immune func-
tion.

6 Claims, No Drawings

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LIR-9, A NOVEL LEUKOCYTE IMMUNOGLOBULIN-LIKE RECEPTOR

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 10/139,662, filed May 2, 2002, now abandoned, which is a divisional of U.S. application Ser. No. 09/310,463, filed May 12, 1999, now U.S. Pat. No. 6,384,203 which is a continuation-in-part of U.S. application Ser. No. 08/842,248, filed Apr. 24, 1997, now U.S. Pat. No. 6,448,035, which are herein incorporated by reference.

REFERENCE TO A SEQUENCE LISTING

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided with a file name of 2624-US-CNT4.txt, a creation date of Dec. 8, 2009, and a size of 169 KB (173,122 bytes). The information in the electronic format of the Sequence Listing is incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

Immune system cellular activity is controlled by a complex network of cell surface interactions and associated signaling processes. When a cell surface receptor is activated by its ligand a signal is sent to the cell, depending upon the signal transduction pathway that is engaged, the signal can be inhibitory or activatory. For many receptor systems cellular activity is regulated by a balance between activatory signals and inhibitory signals. In some of these it is known that positive signals associated with the engagement of a cell surface receptor by its ligand are downmodulated or inhibited by negative signals sent by the engagement of a different cell surface receptor by its ligand.

The biochemical mechanisms of these positive and negative signaling pathways have been studied for a number of known immune system receptor and ligand interactions. Many receptors that mediate positive signaling have cytoplasmic tails containing sites of tyrosine phosphatase phosphorylation known as immunoreceptor tyrosine-based activation motifs (ITAM). A common mechanistic pathway for positive signaling involves the activation of tyrosine kinases which phosphorylate sites on the cytoplasmic domains of the receptors and on other signaling molecules. Once the receptors are phosphorylated, binding sites for signal transduction molecules are created which initiate the signaling pathways and activate the cell. The inhibitory pathways involve receptors having immunoreceptor tyrosine based inhibitory motifs (ITIM) which, like the ITAMs, are phosphorylated by tyrosine kinases. Receptors having these motifs are involved in inhibitory signaling because these motifs provide binding sites for tyrosine phosphatases which block signaling by removing tyrosine from activated receptors or signal transduction molecules. While many of the details of the activation and inhibitory mechanisms are unknown, it is clear that functional balance in the immune system depends upon opposing activatory and inhibitory signals.

One example of immune system activity that is regulated by a balance of positive and negative signaling is B cell proliferation. The B cell antigen receptor is a B cell surface immunoglobulin which, when bound to antigen, mediates a positive signal leading to B cell proliferation. However, B cells also express Fc γ RIIb1, a low affinity IgG receptor. When an antigen is part of an immune complex with soluble immu-

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noglobulin, the immune complex can bind B cells by engaging both the B cell antigen receptor via the antigen and Fc γ RIIb1 via the soluble immunoglobulin. Co-engagement of the Fc γ RIIb1 with the B cell receptor complex downmodulates the activation signal and prevents B cell proliferation. Fc γ RIIb1 receptors contain ITIM motifs which are thought to deliver inhibitory signals to B cells via interaction of the ITIMs with tyrosine phosphatases upon co-engagement with B cell receptors.

The cytolytic activity of Natural Killer (NK) cells is another example of immune system activity which is regulated by a balance between positive signals that initiate cell function and inhibitory signals which prevent the activity. The receptors that activate NK cytotoxic activity are not fully understood. However, if the target cells express cell-surface MHC class I antigens for which the NK cell has a specific receptor, the target cell is protected from NK killing. These specific receptors, known as Killer Inhibitory Receptors (KIRs) send a negative signal when engaged by their MHC ligand, downregulating NK cell cytotoxic activity.

KIRs belong to the immunoglobulin superfamily or the C-type lectin family (see Lanier et al., *Immunology Today* 17:86-91, 1996). Known human NK KIRs are members of the immunoglobulin superfamily and display differences and similarities in their extracellular, transmembrane and cytoplasmic regions. A cytoplasmic domain amino acid sequence common to many of the KIRs is an ITIM motif having the sequence YxxL/V. In some cases, it has been shown that phosphorylated ITIMs recruit tyrosine phosphatases which dephosphorylate molecules in the signal transduction pathway and prevent cell activation (see Burshtyn et al., *Immunity* 4:77-85, 1996). The KIRs commonly have two of these motifs spaced apart by 26 amino acids [YxxL/V(x)₂₆YxxL/V]. At least two NK cell receptors, each specific for a human leukocyte antigen (HLA) C allele (an MHC class I molecule), exist as an inhibitory and an activatory receptor. These receptors are highly homologous in the extracellular portions, but have major differences in their transmembrane and cytoplasmic portions. One of the differences is the appearance of the ITIM motif in the inhibitory receptor and the lack of the ITIM motif in the activating receptor (see Biassoni et al., *Journal. Exp. Med.*, 183:645-650, 1996).

An immunoreceptor expressed by mouse mast cells, gp49B1, also a member of the immunoglobulin superfamily, is known to downregulate cell activation signals and contains a pair of ITIM motifs. gp49B1 shares a high degree of homology with human KIRs (Katz et al., *Cell Biology*, 93: 10809-10814, 1996). Mouse NK cells also express a family of immunoreceptors, the Ly49 family, which contain the ITIM motif and function in a manner similar to human KIRs. However, the Ly49 immunoreceptors have no structural homology with human KIRs and contain an extracellular C-type lectin domain, making them a member of the lectin superfamily of molecules (see Lanier et al., *Immunology Today* 17:86-91, 1996).

Clearly, the immune system activatory and inhibitory signals mediated by opposing kinases and phosphatases are very important for maintaining balance in the immune system. Systems with a predominance of activatory signals will lead to autoimmunity and inflammation. Immune systems with a predominance of inhibitory signals are less able to challenge infected cells or cancer cells. Isolating new activatory or inhibitory receptors is highly desirable for studying the biological signal(s) transduced via the receptor. Additionally, identifying such molecules provides a means of regulating and treating diseased states associated with autoimmunity, inflammation and infection.

For example engaging a newly discovered cell surface receptor having ITIM motifs with an agonistic antibody or ligand can be used to downregulate a cell function in disease states in which the immune system is overactive and excessive inflammation or immunopathology is present. On the other hand, using an antagonistic antibody specific to the receptor or a soluble form of the receptor can be used to block the interaction of the cell surface receptor with the receptor's ligand to activate the specific immune function in disease states associated with suppressed immune function. Conversely, since receptors lacking the ITIM motif send activatory signals once engaged as described above, the effect of antibodies and soluble receptors is the opposite of that just described.

SUMMARY OF THE INVENTION

The present invention provides a new family of immunoreceptor molecules of the immunoglobulin superfamily, designated herein as the Leukocyte Immunoglobulin-Like Receptor (LIR) polypeptides. Within the scope of the present invention are DNA sequences encoding LIR family members and their deduced amino acid sequences disclosed herein. Further included in the present invention are polypeptides encoded by DNA that hybridize to oligonucleotide probes having defined sequences or to DNA or RNA complementary to the probes. The present invention also includes recombinant expression vectors comprising DNA encoding LIR family members. Also within the scope of the present invention are nucleotide sequences which, due to the degeneracy of the genetic code, encode polypeptides that are identical to polypeptides encoded by the nucleic acid sequences described above, and sequences complementary to those nucleotide sequences.

Further, the present invention includes processes for producing polypeptides of the LIR family by culturing host cells transformed with a recombinant expression vector that contains an LIR family member encoding DNA sequence under conditions appropriate for expressing an LIR polypeptide family member, then recovering the expressed LIR polypeptide from the culture.

The invention also provides agonistic and antagonistic antibodies to LIR family proteins.

Further still within the present invention are fusion proteins that include a soluble portion of an LIR family member and the Fc portion of Ig.

Certain autoimmune disorders are associated with the failure of a negative signaling LIR to downregulate cell function. Such disorders may be treated by administering a therapeutically effective amount of an agonistic antibody or ligand of one or more a LIR family member to a patient afflicted with such a disorder. Disorders mediated by disease states associated with suppressed immune function can be treated by administering a soluble form of the negative signaling LIR. Conversely, disorders mediated by diseases associated with failure of a activatory signaling LIR can be treated by administering an agonistic antibody of the activatory receptor. Disorders mediated by states associated with autoimmune function can be treated by administering a soluble form of the activatory receptor.

DETAILED DESCRIPTION OF THE INVENTION

A viral glycoprotein having a sequence similarity to MHC class I antigens has been used to isolate and identify a new polypeptide, designated LIR-P3G2, and several members of a new family of cell surface polypeptides that has been desig-

nated the LIR polypeptide family. The present invention encompasses isolated nucleic acid molecules encoding LIR polypeptides, and further encompasses isolated LIR polypeptides. Exemplary nucleic acids encoding LIR polypeptides according to the present invention include those nucleotide sequences shown in SEQ ID NOS:1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 29, 31, 33, 35 and 37, and exemplary LIR polypeptide sequences are shown in SEQ ID NOS:2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38.

The LIR polypeptide family members possess extracellular regions having immunoglobulin-like domains, placing the members in a new subfamily of the immunoglobulin superfamily. While the LIR family members are characterized as having very similar extracellular portions, the family includes three groups of polypeptides that are distinguishable by their transmembrane regions and their cytoplasmic regions. One group of the LIR polypeptides has a transmembrane region that includes a positively charged residue and a short cytoplasmic tail and a second group has a nonpolar transmembrane region and a long cytoplasmic tail. A third group includes polypeptides expressed as soluble proteins having no transmembrane region or cytoplasmic tail. One of the LIR proteins has characteristics of both groups one and two, and may represent a fourth group. A number of recent reports have described nucleic acid molecules having sequences related to the LIR family of proteins (Hillier et al., GenBank Accession Number N95687, Apr. 9, 1996; Colonna, M., GenBank Accession Nos. AF041261 and AF041262, Jan. 7, 1999; Lamerdin et al., GenBank Accession No. AC006293, Jan. 6, 1999; Steffans et al., GenBank Accession Nos. AH007466 and AH007465, Mar. 4, 1999; Cosman et al., *Immunity* 7:273-282 (1997); Borges et al., *J. Immunol.* 159:5192-96 (1997); Samaridis and Colonna, *Eur. J. Immunol.* 27:660-665 (1997); Colonna et al., *J. Exp. Med.* 186:1809-1818 (1997); Wagtmann et al., *Curr. Biol.* 7:615-618 (1997); Rojo et al., *J. Immunol.* 158:9-12 (1997); Arm et al., *J. Immunol.* 159:2342-2349 (1997); Cella et al., *J. Exp. Med.* 185:1743-51 (1997); Torkar et al., *Eur. J. Immunol.* 28:3959-67 (1998); Yamashita et al., *J. Biochem.* 123:358-68 (1998); WO 98/31806; WO 98/24906; WO 98/09638).

The LIR polypeptides encompassed by the subject invention contain at least one Ig-like domain in the extracellular region of the protein, preferably contain either two or four Ig-like domains in the extracellular region. Some LIR polypeptides may contain more than four Ig-like domains. An Ig-like domain is a structural unit that has been identified in a wide variety of cellular proteins. Ig-like domains contain a common fold that forms a sandwich of two β sheets that is stabilized by a characteristic intrachain disulfide bond. Ig-like domains are readily recognizable by reference to a large body of knowledge concerning this structural entity (see, e.g., Williams and Barclay, *Ann. Rev. Immunol.* 6:381-405 (1988)). Typically, Ig-like domains contain about 100 amino acids, although the number of amino acids may vary, e.g., from about 85 to 105 amino acids. Molecules that exhibit Ig-like domains generally play a recognition role at the cell surface, often mediating cell-cell interactions in a variety of biological systems.

LIR-P3G2 (SEQ ID NO:2) is expressed by a variety of cells and recognizes HLA-B44 molecules, HLA-A2 MHC molecules and the alleles described in Example 14. Another LIR family member, designated LIR-pbm8 (SEQ ID NO:9) is expressed by a variety of cells and also recognizes a number of MHC class I molecules. By analogy with known molecules, LIR-P3G2, LIR-pbm8 and LIR members have a role in immune recognition and self/nonself discrimination.

Examples 1-3 below describe isolating cDNA encoding P3G2 (LIR-P3G2) and a substantially identical polypeptide designated 18A3 (LIR-18A3). Briefly, the LIR-P3G2 family member was isolated by first expressing UL18, a Class I MHC-like molecule and using UL18 to isolate and identify P3G2 and 18A3, which are closely related and probably are variants of the same gene, which is designated "LIR-1." The nucleotide sequences of the isolated P3G2 cDNA and 18A3 cDNA are presented in SEQ ID NO:1 and SEQ ID NO:3, respectively. The amino acid sequences encoded by the cDNA presented in SEQ ID NO:1 and SEQ ID NO:3 are presented in SEQ ID NO:2 and SEQ ID NO:4, respectively. The P3G2 amino acid sequence (SEQ ID NO:2) has a predicted extracellular domain of 458 amino acids (1-458) including a signal peptide of 16 amino acids (amino acids 1-16); a transmembrane domain of 25 amino acids (amino acids 459-483) and, a cytoplasmic domain of 167 amino acids (amino acids 484-650). The extracellular domain includes four immunoglobulin-like domains. Ig-like domain I includes approximately amino acids 17-118; Ig-like domain II includes approximately amino acids 119-220; Ig-like domain III includes approximately amino acids 221-318; and Ig-like domain IV includes approximately amino acids 319-419. Significantly, the cytoplasmic domain of this polypeptide includes four ITIM motifs, each having the consensus sequence of YxxL/V. The first ITIM motif pair is found at amino acids 533-536 and 562-565 and the second pair is found at amino acids 614-617 and 644-647. This feature is identical to the ITIM motifs found in KIRs except that KIRs contain only one pair of ITIM motifs.

The 18A3 amino acid sequence (SEQ ID NO:4) has a predicted extracellular region of 459 amino acids (1-459) including a signal peptide of 16 amino acids (amino acids 1-16); a transmembrane domain of 25 amino acids (amino acids 460-484) and a cytoplasmic domain of 168 amino acids (485-652). The 18A3 amino acids sequence (SEQ ID NO:4) is substantially identical to that of P3G2 (SEQ ID NO:2) except that 18A3 has two additional amino acids (at amino acid 438 and 552) and 18A3 possesses an isoleucine residue at amino acid 142 in contrast to a threonine residue for P3G2. Additionally, 18A3 has a serine residue at amino acid 155 and P3G2 has an isoleucine at 155. Finally, the 18A3 polypeptide has a glutamic acid at amino acid 627 and P3G2 has a lysine at 625 which is aligned with the 627 residue of the 18A3 polypeptide. The four ITIM motifs in the 18A3 cytoplasmic domain are at amino acids 534-537 and 564-567 and at 616-619 and 646-649. Glycosylation sites occur at the amino acid triplet Asn-X-Y, where X is any amino acid except Pro and Y is Ser or Thr. Thus, potential glycosylation sites on LIR-P3G2 occur at amino acids 140-142; 281-283; 302-304; and 341-343. Sites on LIR-18A3 are at 281-283; 302-304; and 341-343. The features of these encoded polypeptides are consistent with type I transmembrane glycoproteins.

Examples 8-10 describe isolating and identifying eight additional LIR polypeptide family members by probing cDNA libraries for plasmids that hybridize to a probe obtained from DNA encoding the extracellular region of LIR-P3G2. The nucleotide sequences (cDNA) of the isolated LIR family members are presented in SEQ ID NO:7 (designated pbm25, or LIR-4), SEQ ID NO:9 (designated pbm8, or LIR-2), SEQ ID NO:11 (designated pbm36-2, or LIR-6b), SEQ ID NO:13 (designated pbm36-4, or LIR-6a); SEQ ID NO:15 (designated pbmhh, or LIR-7); SEQ ID NO:17 (designated pbm2, or LIR-5), SEQ ID NO:19 (designated pbm17, or LIR-3) and SEQ ID NO:21 (designated pbmnew, or LIR-8). The amino acid sequences encoded thereby are presented in

SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO: 18, SEQ ID NO: 20 and SEQ ID NO:22, respectively.

Example 15 describes the isolation of LIR-9 m1 (SEQ ID NOS:29, 30), LIR-9 m2 (SEQ ID NO:31, 32), LIR-9s1 (SEQ ID NO:33, 34), and LIR-9s2 (SEQ ID NO:35, 36), which are four alternatively spliced variants of LIR-9, another new member of the LIR family. The first step in identifying these LIR-9 group of clones was the isolation of a short cDNA clone that was obtained from a human dendritic cell library and whose sequence analysis indicated that it had significant homology with the LIR family, particularly with the sequences shown in SEQ ID NOS:11, 13 and 15. Using PCR primers based on this clone, further cloning efforts yielded four full-length cDNAs corresponding to LIR-9 m1, -9 m2, -9s1 and -9s2. LIR-9 m1 and LIR-9 m2 are transmembrane proteins that differ by 12 amino acids that are found in the extracellular region of LIR-9 m1, but that are absent from LIR9 m2. These 12 amino acids correspond to amino acids 29-40 of SEQ ID NO:30. LIRs-9s1 and -9s2 do not contain a transmembrane domain, thus encode soluble versions of LIR-9. The LIR-9s1 polypeptide (SEQ ID NO:34) includes the 12 amino acid insert that is present in LIR-9 m1. Amino acids 1-238 of LIR-9s1 (SEQ ID NO:34) and LIR-9 m1 (SEQ ID NO:30) are identical, but the remainder of the LIR-9s1 sequence is not identical to the corresponding region of LIR-9 m1. Amino acids 1-226 of LIR-9s2 (SEQ ID NO:36) are identical to the first 226 amino acids of LIR-9 m2 (SEQ ID NO:32), but the remaining amino acid sequence of LIR-9s2 diverges from that of LIR-9 m2.

The same PCR primers that were used to isolate the LIR-9 clones yielded an additional cloned LIR cDNA that has been designated LIR-10 (SEQ ID NOS:37 and 38). By comparing the nucleotide sequence of LIR-10 with the most closely related LIRs that were previously identified, i.e. with SEQ ID NOS:13 and 15, it has been determined that the LIR-10 cDNA is an incomplete clone that lacks sequences located at the 5' end of the corresponding mRNA, including the 5' untranslated region, and nucleotides encoding the first 26 amino acids of the LIR-10 protein.

The identified extracellular, transmembrane and cytoplasmic regions for the polypeptides of LIR family members shown in SEQ ID NOS:10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38 are presented below. The polypeptides presented in SEQ ID NOS:8, 34 and 36 are soluble proteins having no transmembrane or cytoplasmic regions. As will be understood by the skilled artisan, the transmembrane region of P3G2 and 18A3 described above and those of LIR polypeptide family members presented below are identified in accordance with conventional criteria for identifying hydrophobic domains associated with such regions. Accordingly, the precise boundaries of any selected transmembrane region may vary from those presented herein. Typically, the transmembrane domain does not vary by more than five amino acids on either end of the domain as described herein. Computer programs known in the art and useful for identifying such hydrophobic regions in proteins are available.

The polypeptide presented in SEQ ID NO:8 (LIR-pbm25) has an extracellular domain that includes the entire amino acid sequence of amino acids 1-439 and a signal peptide of amino acids 1-16. The amino acid sequence presented in SEQ ID NO:10 (LIR-pbm8) has a predicted extracellular region of 458 amino acids (1-458) including a 16 amino acid signal peptide (amino acids 1-16); a transmembrane domain that includes amino acids 459-483; and a cytoplasmic domain that includes amino acids 484-598. The extracellular domain

includes four immunoglobulin-like domains and the cytoplasmic domain includes an ITIM motif at amino acids 533-536 and 562-565.

The amino acid sequence presented in SEQ ID NO:12 (LIR-pbm36-2) has a predicted extracellular domain of amino acids including a 16 amino acid signal peptide of from amino acids 1-16; a transmembrane domain which includes amino acids 262-280 and a cytoplasmic domain of from amino acids 281-289. The transmembrane domain includes a charged arginine residue at 264 and the cytoplasmic domain is short, having only a length of only 9 amino acids.

The amino acid sequence presented in SEQ ID NO:14 (LIR-pbm36-4) has a predicted extracellular domain of amino acids 1-461 including a signal peptide from amino acids 1-16; a transmembrane domain that includes amino acids 462-480 and possesses a charged arginine residue at amino acid 464; and a cytoplasmic domain that includes amino acids 481-489. SEQ ID NO:14 is nearly identical to that of SEQ ID NO:12 except that it possesses four immunoglobulin domains in contrast to the two domains found in the extracellular region of SEQ ID NO:12. The amino acid sequences presented in SEQ ID NO:12 and SEQ ID NO:14 are likely proteins encoded by alternatively spliced transcripts from the same gene.

The amino acid sequence presented in SEQ ID NO:16 (LIR-pbmhh) has a predicted extracellular domain that includes amino acids 1-449 and a signal peptide from amino acids 1-16; a transmembrane domain that includes amino acids 450-468 with a charged arginine residue at amino acid 452; and a cytoplasmic domain that includes amino acids 469-483. The cytoplasmic domain is short with a length of 15 amino acids. The extracellular domain includes four immunoglobulin-like domains.

The amino acid sequence presented in SEQ ID NO:18 (LIR-pbm2) has a predicted extracellular region that includes amino acids 1-259 and a signal peptide of amino acids 1-16; a transmembrane domain that includes amino acids 260-280; and a cytoplasmic domain that includes amino acids 281-448. This LIR family member has cytoplasmic domain which includes an ITIM motif at amino acids 412-415 and 442-445. The extracellular domain includes two immunoglobulin-like domains.

The amino acid sequence presented in SEQ ID NO:20 (LIR-pbm17) has a predicted extracellular domain of amino acids 1-443 that includes a signal peptide of amino acids 1-16; a transmembrane domain which includes amino acids 444-464; and a cytoplasmic domain of amino acids 465-631. The extracellular domain has four immunoglobulin-like domains. SEQ ID NO:20 has two pairs of ITIM YxxL/V motifs in the cytoplasmic domain. A first pair is at amino acids 514-517 and 543-546, and a second pair is at amino acids 595-598 and 625-628.

The amino acid sequence presented in SEQ ID NO:22 (LIR-pbmnew) has a predicted extracellular domain of amino acids 1-456 including a signal peptide of amino acids 1-16; a transmembrane domain which includes amino acids 457-579; and a cytoplasmic domain of amino acids 580-590. The extracellular domain includes four immunoglobulin-like domains. SEQ ID NO:22 has an ITIM motif at amino acids 554-557 and 584-587.

The LIR-9 m1 protein has an extracellular domain located at amino acids 1-262 of SEQ ID NO:30, including a signal peptide at amino acids 1-34 of SEQ ID NO:30. Amino acids 263-284 of SEQ ID NO:30 define the transmembrane region of LIR-9 m1, and amino acids 285-299 of SEQ ID NO:30 form the cytoplasmic region. For LIR-9 m2, the extracellular region corresponds to amino acids 1-250 of SEQ ID NO:32,

including a signal sequence at amino acids 1-35 of SEQ ID NO:32, a transmembrane region at residues 251-272 of SEQ ID NO:32, and a cytoplasmic region at amino acids 273-287 of SEQ ID NO:32. LIR-9s1 (SEQ ID NO:34) and LIR-9s2 (SEQ ID NO:36) consist, respectively, of 265 and 253 amino acids, with their signal sequences being found at amino acids 1-34 of SEQ ID NO:34, and amino acids 1-35 of SEQ ID NO:36.

For LIR-10, amino acids 1-393 of SEQ ID NO:38 correspond to most of the extracellular portion of the LIR-10 protein, though the coding sequences for about 26 amino acids at the amino terminus of this protein, including the signal peptide, are believed to be missing from the LIR-10 cDNA clone that is described herein. The transmembrane region of LIR-10 is defined by amino acids 394-417 of SEQ ID NO:38, and the intracellular region by amino acids 418-449. A single ITIM motif is located at amino acids 438-443 of SEQ ID NO:38.

The amino acid sequences presented in SEQ ID NO: 2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38 reveal that the LIR family, with the exception of LIR-10, can be categorized into three groups of polypeptides. One group includes the polypeptides of SEQ ID NOS:12, 14, 16, 30 and 32, which are distinguishable by a charged arginine residue in their transmembrane regions and their short cytoplasmic regions. A second group includes SEQ ID NO: 2, 4, 10, 18, 20 and 22 which are distinguishable by their hydrophobic cytoplasmic domains and the presence of one or more ITIM motifs in their cytoplasmic regions. A third group includes the polypeptides of SEQ ID NOS: 8, 34 and 36, which are expressed as soluble polypeptides and have no transmembrane or cytoplasmic regions. These soluble polypeptides may function to block the interactions of cell surface family members with their receptors. Alternatively, the soluble polypeptides may act as an activatory signal when bound to the receptor. Like the members of group one, LIR-10 has a relatively short cytoplasmic domain and a charged residue in its transmembrane domain, though its charged residue is histidine instead of arginine. However, LIR-10 also has an ITIM motif in its cytoplasmic domain, like the members of group two. Thus, LIR-10 has some of the characteristics of both groups one and two, and may represent a fourth group of LIR proteins. The LIR polypeptides are characterized generally by the ability of their encoding DNA to hybridize to DNA encoding the P3G2 extracellular region.

The invention should be understood to encompass isolated nucleic acid molecules encoding LIR polypeptides having the amino acid sequences shown in SEQ ID NOS:2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38. In one embodiment of the invention, these nucleic acid molecules have the nucleic acid sequences shown in SEQ ID NOS:1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 29, 31, 33, 35 and 37.

The extracellular regions of the LIR family member proteins presented in SEQ ID NO:2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38 have a high degree of homology, which varies from 59%-84. Several of the LIR isolates are closely related, thus must represent allelic variants or splicing variants. For example, the extracellular regions of SEQ ID NO:12 and SEQ ID NO:14 share sequence homology which is close to 100%, thus indicating that these polypeptides derive from the same gene. In addition, SEQ ID NOS:2 and 4 share sequence homology that is in excess of 95%, thus probably represent two alleles of the same gene. Moreover, as discussed above, the extracellular regions of SEQ ID NOS: 30, 32, 34 and 36 are nearly identical, thus indicating that these four proteins derive from mRNAs that are splicing variants.

While sharing some structural similarities with other members of the immunoglobulin superfamily, the LIR family members have limited homology to other members of the immunoglobulin superfamily. Molecules having the closest structural similarity to the LIRs are the human KIRs and mouse gp49. However, LIR extracellular regions share only a 38-42% identity with the extracellular regions of NKAT3 and p58 C1-39, respectively. The extracellular regions of the LIR family members are only 35-47% homologous with that of mouse gp49. In contrast, KIRs in general are known to share at least a 80% amino acid identity, with NKAT3 and p58 CL-39 being 81% homologous. Additionally, none of the known KIR molecules has four extracellular immunoglobulin domains which is characteristic of all but two of the known LIR family members. In view of the high sequence homology among the LIR related polypeptides disclosed herein and their relatively low homology with KIRs, the LIR polypeptides are members of a new family of immunoregulators.

An analysis of the amino acid sequences of the LIR polypeptides reveals that specific stretches of amino acids of the LIR polypeptides are highly conserved. One conserved region is a sequence of 46 amino acids found at amino acids 5-50 of SEQ ID NO:2. A data base search determined that the LIR family members differ substantially from the most structurally similar prior art polypeptides in this LIR conserved region. The data base search and structural analysis was performed using BLAST NB1, a local alignment search tool for searching data bases and aligning amino acid sequences to determine identities and variations in a given sequence. The BLAST NB1 software is accessible on the internet at <http://www3.ncbi.nlm.nih.gov/entrez/blast>. The BLAST NB1 search for sequences having homology to the sequence of amino acids 5 to 50 of SEQ ID NO:2 found that the most structurally similar proteins are FcγRII, gp49B form 2, and gp49B form 1 having identities with amino acids 5 to 50 of SEQ ID NO:2 of 63%, 67%, and 67% respectively. This contrasts with an LIR family identity with amino acids 5 to 50 of SEQ ID NO:2 which ranges from about 71% to 100%. Specifically, LIR family members of the present invention contain conserved regions near their amino termini having the following identities with amino acids 5-50 of SEQ ID NO:2: SEQ ID NO:8 has a 96% identity; SEQ ID NO:10 has a 90% identity; SEQ ID NO:12 has a 96% identity; SEQ ID NO:14 has a 91% identity; SEQ ID NO:16 has a 97% identity; SEQ ID NO:18 has a 77% identity; SEQ ID NO:20 has an 80% identity; SEQ ID NO:22 has an 80% identity; SEQ ID NO:30 has a 78% identity; SEQ ID NO:32 has a 71% identity; SEQ ID NO:34 has a 78% identity; SEQ ID NO:36 has a 71% identity. This conserved region appears to be present also in LIR-10 (SEQ ID NO:38), but is incomplete due to the LIR-10 cDNA clone disclosed herein being truncated at its 5' end.

Sequence identity as used herein is the number of aligned amino acids which are identical, divided by the total number of amino acids in the shorter of the two sequences being compared. A number of computer programs are available commercially for aligning sequences and determining sequence identities and variations. These programs provide identity information based upon the above stated definition of identity. One suitable computer program is the GAP program, version 6.0, described by Devereux et al. (*Nucl. Acids Res.* 12:387, 1984) and available from the University of Wisconsin Genetics Computer Group (UWGCG). The GAP program utilizes the alignment method of Needleman and Wunsch (*J. Mol. Biol.* 48:443, 1970), as revised by Smith and Waterman (*Adv. Appl. Math* 2:482, 1981). The preferred default parameters for the GAP program include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-

identities) for nucleotides or amino acids, and the weighted comparison matrix of Gribskov and Burgess, *Nucl. Acids Res.* 14:6745, 1986, as described by Schwartz and Dayhoff, eds., *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, pp. 353-358, 1979; (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps. Another similar program, also available from the University of Wisconsin as part of the GCG computer package for sequence manipulation is the BESTFIT program.

In another aspect, the polypeptides of the present invention have conserved regions which are uniquely characterized as having the amino acid sequence (SEQ ID NO:28):

Leu Xaa_a Leu Ser Xaa_b Xaa_c Pro Arg Thr Xaa_d Xaa_e Gln Xaa_f Gly Xaa_g Xaa_h Pro Xaa_i Pro Thr Leu Trp Ala Glu Pro Xaa_j Ser Phe Ile Xaa_k Xaa₇₀ Ser Asp Pro Lys Leu Xaa_l Leu Val Xaa_m Thr Gly

where Xaa_a is Gly or Arg; Xaa_b is Leu or Val; Xaa_c is Gly or Asp; Xaa_d is His Arg or Cys; Xaa_e is Val or Met; Xaa_f is Ala or Thr; Xaa_g is His Pro or Thr; Xaa_h Leu Ile or Phe; Xaa_i is Gly Asp or Ala; Xaa_j is Thr Ile Ser or Ala; Xaa_k is Gly or Val; Xaa_m is Met or Ala; and Xaa₇₀ is a sequence of 70 amino acids.

As mentioned above, certain LIR family members have ITIM motifs (YxxL/V₂₅₋₂₆ YxxL/V) in their cytoplasmic domains. It is known that many immune regulating receptors such as KIRs, CD22, FcγRIIb 1 also have ITIMs in their cytoplasmic domain and function to send inhibitory signals which down regulate or inhibit cell function. It has been shown that these receptors associate with SHP-1 phosphatase via binding to the ITIM motifs. Recruitment of the SHP-1 phosphatase by the receptor appears to be required for intracellular signaling pathways that regulate the inhibitory function of the receptors. The experiment described in Example 11 demonstrates that LIR-P3G2 and LIR-pbm8 polypeptides associate with SHP-1 phosphatase upon phosphorylation and generate inhibitory signals through monocyte activation pathways. It is known that many immune regulating receptors such as KIRs, CD22, FcγRIIb1 have ITIMs in their cytoplasmic domain and function to send inhibitory signals which down regulate or inhibit cell function. Thus, by analogy with KIRs, CD22 and FcγRIIb1, LIR family members presented in SEQ ID NO:2, 4, 10, 18, 20, 22 and 38 that have ITIM motifs deliver an inhibitory signal via the interaction of its ITIM with SHP-1 tyrosine phosphatase, or other tyrosine phosphatases, when the LIR is coligated with an appropriate receptor. Also by analogy with immunoregulatory receptors possessing ITIMs, LIR family members have a regulatory influence on humoral, inflammatory and allergic responses.

The LIR family members presented in SEQ ID NO:12, 14, 16, 30 and 32 have relatively short cytoplasmic domains, have transmembrane regions possessing at least one charged residue, and do not possess the ITIM motif. By analogy with membrane proteins that lack ITIM motifs and have charged transmembrane regions, these family members mediate stimulatory or activatory signals to cells. For example, membrane bound proteins containing a charged residue in the transmembrane regions are known to associate with other membrane-bound proteins that possess cytoplasmic tails having motifs known as immunoreceptor tyrosine-based activation motifs (ITAM). Upon association, the ITAMs become phosphorylated and propagate an activation signal.

The LIR polypeptide designated LIR-P3G2 is expressed on the surface of transfected or normal cells. This is evidenced by the results of the experiments described in Example 3 and Example 5 in which flow cytometry and precipitation techniques demonstrate that LIR-P3G2 is found

on monocytes, a subpopulation of NK cells, and B cells. P3G2 was detected on small subset of T cells. P3G2 is expressed as a 110-120 kDa glycoprotein. Since P3G2 has four potential glycosylation sites, the molecular size of this protein will vary with the degree of its glycosylation. Glycosylation sites occur at the amino acid triplet Asn-X-Y, where X is any amino acid except Pro and Y is Ser or Thr. Potential glycosylation sites on P3G2 occur at amino acids 139-141; 280-282; 302-304; and 340-342.

P3G2-LIR isolated as described in Example 3 was tested for its ability to bind to cell surface ligands distinct from UL18. As demonstrated by the experimental results detailed in Example 7, P3G2 binds HLA-B 44 and HLA-A2, class I MHC antigens. Similarly, as demonstrated in Example 14, LIR-P3G2 and LIR-pbm8 bind to a variety of HLA-A, -B, and -C alleles and recognize a broad spectrum of MHC class I specificities. Since Class I MHC molecules play a central role in immune surveillance, self/non-self discrimination, the immune response to infection etc., the LIR-P3G2 and LIR-pbm8 polypeptides have a role in regulation of immune responses. It is known that NK cytolytic activity for killing tumor cells and cells infected with a virus is regulated by a delicate modulation of activatory and inhibitory signals. It has been shown that receptors specific for the same HLA class I molecules to which LIR-P3G2 and LIR-pbm8 bind may be activatory or inhibitory in their triggering mechanism. By analogy, LIR-P3G2 and LIR-pbm8, which bind MHC class I molecules, play a role in balancing immune system cell activity and are useful in treating disease states in which the immune system balance is disrupted.

Within the scope of the present invention are polypeptides which include amino acid sequences encoded by DNA that hybridizes to LIR-P3G2 extracellular DNA probes under moderate to highly stringent conditions as taught herein. Probes that hybridize to DNA that encode polypeptides of the present invention include probes which encompass nucleotides 310-1684 of SEQ ID NO:1 or fragments thereof. Fragments of SEQ ID NO:1 utilized as hybridization probes are preferably greater than 17 nucleotides in length, and more typically are greater than 20 nucleotides in length, and may include nucleotides 358-1684; nucleotides 322-459 (encoding LIR conserved sequence); or DNA or RNA sequences complementary to SEQ ID NOS:5, 6, 23, 24, 27 and 1 or fragments thereof. Fragments of SEQ ID NOS:5, 6, 23, 24 and 27 include these sequences without the restriction sites. The nucleotide sequences described herein also can be used to design PCR primers, for which a convenient length is about 17-30 nucleotides.

Conditions for hybridization may be moderately stringent conditions described in, for example, in Sambrook et al, *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, 1989, which is hereby incorporated by reference (see, e.g., Vol. 1, pp 1.101-104). Conditions of moderate stringency, as defined by Sambrook et al., include, for example, the use of a prewashing solution containing 5×SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0) and hybridization conditions of about 55° C. in 5×SSC, incubated overnight. Highly stringent conditions include higher temperatures of hybridization and washing. The skilled artisan will recognize that a given degree of stringency may be maintained while varying the hybridization or wash temperature or composition of the hybridization buffer in accord with formulae known to those in the art (e.g., see Sambrook et al., 9.50-9.51 and 11.45-11.47). Such formulae take into account factors such as the length of the probe, the G+C content of the probe, salt concentration of the hybridization buffer. If desired, formamide may be added to the hybridization buffer,

which permits the use of lower hybridization temperatures (e.g., see Sambrook et al., 9.50-9.51).

Preferred embodiments include amino acid sequences encoded by DNA that hybridizes to probes of the extracellular region of LIR-P3G2 having at least 17 nucleotides. Preferred hybridizing conditions include an incubation temperature of 63° C. for 16 hours in a solution of Denhart's solution, 0.05 M TRIS at pH 7.5, 0.9 M NaCl, 0.1% sodium pyrophosphate, 1% SDS and 200 µg/mL salmon sperm DNA, followed by washing with 2×SSC at 63° C. for one hour and then washing with 1×SSC at 63° C. for one hour. However, as explained above, one skilled in the art can devise other hybridization conditions that produce the same degree of stringency. Generally, stringent hybridization conditions involve a combination of buffer and incubation temperature that supports the formation of specific, i.e., well-matched duplexes while still allowing the formation of stable duplexes at an acceptable rate. Conditions of reduced stringency permit the formation of stable duplexes containing a higher degree of mismatched base pairs than can form under more stringent conditions.

Stringent hybridization conditions for PCR primers can be achieved, for example, by hybridizing labeled probes to filter-bound target nucleic acid overnight at 50-55° C. in aqueous buffer containing 5×SSC or 6×SSC (1×SSC=0.15 M NaCl, 0.015 M sodium citrate), followed by washes in 6×SSC at 50-55° C. However, the skilled artisan will recognize that stringent hybridization conditions for oligonucleotide probes will vary, depending on the length, base composition and sequence of the probe (e.g., see Sambrook et al., 11.45-11.49).

The present invention includes polypeptides having amino acid sequences that differ from, but are highly homologous to, those presented in SEQ ID NOS:2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38. Examples include, but are not limited to, homologs derived from other mammalian species, variants (both naturally occurring variants and those generated by recombinant DNA technology), and LIR P3G2 and LIR family member fragments that retain a desired biological activity. Preferably, such polypeptides exhibit a biological activity associated with the LIR polypeptides described in SEQ ID NOS:2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38, and comprise an amino acid sequence that is at least 80% identical to any of the amino acid sequences of the signal peptide and extracellular domains of the polypeptides presented in SEQ ID NOS:2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38. Preferably such polypeptides are at least 90% identical to any of the amino acid sequences of the signal peptide and extracellular domains of the polypeptides presented in SEQ ID NOS: 2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38. Determining the degree of identity between polypeptides can be achieved using any algorithms or computer programs designed for analyzing protein sequences. The commercially available GAP program described below is one such program. Other programs include the BESTFIT and GCG programs which are also commercially available.

Within the scope of the present invention are LIR polypeptide fragments that retain a desired biological property of an LIR polypeptide family member such as binding to MHC class I or other ligand. In one such embodiment, LIR polypeptide fragments are soluble LIR polypeptides comprising all or part of the extracellular domain, but lacking the transmembrane region that would cause retention of the polypeptide on a cell membrane. Soluble LIR polypeptides are capable of being secreted from the cells in which they are expressed. Advantageously, a heterologous signal peptide is fused to the N-terminus such that the soluble LIR is secreted upon expression. Soluble LIR polypeptides include extracellular domains

incorporating the signal peptide and those in which the signal peptide is cleaved signal peptide.

The use of soluble forms of a LIR family member is advantageous for certain applications. One such advantage is the ease of purifying soluble forms from recombinant host cells. Since the soluble proteins are secreted from the cells, the protein need not be extracted from cells during the recovery process. Additionally, soluble proteins are generally more suitable for intravenous administration and can be used to block the interaction of cell surface LIR family members with their ligands in order to mediate a desirable immune function.

Further encompassed within the present invention are soluble LIR polypeptides, which may include the entire extracellular domain or any desirable fragment thereof, including extracellular domains that exclude signal peptides. Thus, for example, soluble LIR polypeptides include amino acids x_1 -458 of SEQ ID NO:2, where x_1 is amino acids 1 or 17; amino acids x_2 -459 of SEQ ID NO:4, where x_2 is amino acid 1 or 17; amino acids x_3 -439 of SEQ ID NO:8, where x_3 is amino acid 1 or 17; amino acids x_4 -458 of SEQ ID NO:10, where x_4 is amino acid 1 or 17; amino acids x_5 -241 of SEQ ID NO:12, where amino acid x_5 is amino acid 1 or 17; amino acids x_6 -461 of SEQ ID NO:14, where x_6 is amino acid 1 or 17; amino acids x_7 -449 of SEQ ID NO:16, where x_7 is amino acid 1 or 17; amino acids x_8 -259 of SEQ ID NO:18, where x_8 is amino acid 1 or 17; amino acids x_9 -443 of SEQ ID NO:20, where x_9 is amino acid 1 or 17; amino acids x_{10} -456 of SEQ ID NO:22, where x_{10} is amino acid 1 or 17; amino acids x_{11} -262 of SEQ ID NO:30, where x_{11} is amino acid 1 or 35; amino acids x_{12} -250 of SEQ ID NO:32, where x_{12} is amino acid 1 or 36; amino acids x_{13} of SEQ ID NO:34, where x_{13} is amino acid 1 or 35; amino acids x_{14} of SEQ ID NO:36, where x_{14} is amino acid 1 or 36; and amino acids 1-393 of SEQ ID NO:38. The above identified soluble LIR polypeptides include LIR extracellular regions that include and exclude signal peptides. Also encompassed herein are LIRs that lack a transmembrane and cytoplasmic region, such as SEQ ID NOS:8, 34 and 36. Additional soluble LIR polypeptides include fragments of the extracellular domains of family members that retain a desired biological activity, such as binding to ligands that include MHC class I molecules.

LIR family member fragments, including soluble polypeptides, may be prepared by any of a number of conventional techniques. A DNA sequence encoding a desired LIR polypeptide encoding fragment may be subcloned into an expression vector for production of the LIR polypeptide fragment. The selected encoding DNA sequence advantageously is fused to a sequence encoding a suitable leader or signal peptide. The desired LIR member encoding DNA fragment may be chemically synthesized using known DNA synthesis techniques. DNA fragments also may be produced by restriction endonuclease digestion of a full length cloned DNA sequence, and isolated by electrophoresis on an appropriate gel. If necessary, oligonucleotides that reconstruct the 5' or 3' terminus to a desired point may be ligated to a DNA fragment generated by restriction enzyme digestion. Such oligonucleotides may additionally contain a restriction endonuclease cleavage site upstream of the desired coding sequence, and position an initiation codon (ATG) at the N-terminus of the coding sequence.

Another technique useful for obtaining a DNA sequence encoding a desired protein fragment is the well-known polymerase chain reaction (PCR) procedure. Oligonucleotides which define the termini of the desired DNA are used as primers to synthesize additional DNA from a desired DNA template. The oligonucleotides may also contain recognition sites for restriction endonucleases, to facilitate inserting the

amplified DNA fragment into an expression vector. PCR techniques are described, for example, in Saiki et al., *Science* 239:487 (1988); *Recombinant DNA Methodology*, Wu et al., eds., Academic Press, Inc., San Diego (1989), pp. 189-196; and *PCR Protocols: A Guide to Methods and Applications*, Innis et al., eds., Academic Press, Inc. (1990).

The LIR nucleic acid molecules of the present invention include isolated cDNA, chemically synthesized DNA, DNA isolated by PCR, cloned genomic DNA, and combinations thereof. Genomic LIR family DNA may be isolated by hybridization to the LIR family cDNA disclosed herein using standard techniques. Isolated RNA transcribed from LIR family DNA molecules is also encompassed by the present invention.

Within the scope of the present invention are DNA fragments such as LIR polypeptide coding regions and DNA fragments that encode soluble polypeptides. Examples of DNA fragments that encode soluble polypeptides include DNA that encodes entire extracellular regions of LIR family members and DNA that encodes extracellular region fragments such as regions lacking the signal peptide. More specifically, the present invention includes nucleotides 310-2262 of SEQ ID NO:1 (P3G2 coding region); nucleotides x_1 -1683 of SEQ ID NO:1, where x_1 is 310 or 358 (encoding the P3G2 extracellular domain); nucleotides 168-2126 of SEQ ID NO:3 (the 18A3 coding region) and nucleotides x_2 -1544 of SEQ ID NO:3, where x_2 is 168 or 216 (the 18A3 extracellular domain coding region); nucleotides x_3 -1412 of SEQ ID NO:7, where x_3 is 93 or 141 (the pbm25 coding region and extracellular region); nucleotides 184-1980 of SEQ ID NO:9, (the pbm8 coding region) and nucleotides x_4 -1557 of SEQ ID NO:9, where x_4 is 184 or 232 (the pbm8 extracellular domain coding region); nucleotides 171-1040 of SEQ ID NO:11 (pbm36-2 coding region) and nucleotides x_5 -878 of SEQ ID NO:11, where x_5 is 171 or 219 (encoding the pbm36-2 extracellular domain); nucleotides 183-1652 of SEQ ID NO:13 (coding region for pbm36-4) and nucleotides x_6 -1565 of SEQ ID NO:13, where x_6 is 183 or 231 (encoding the pbm36-4 extracellular domain); nucleotides 40-1491 of SEQ ID NO:15 (the pbmhh coding region) and nucleotides x_7 -1386 of SEQ ID NO:15, where x_7 is 40 or 88 (encoding the pbmhh extracellular domain); nucleotides 30-1376 of SEQ ID NO:17 (the pbm2 coding region) and nucleotides x_8 -806 of SEQ ID NO:17, where x_8 is 30 or 78 (encoding the pbm2 extracellular region); nucleotides 66-1961 of SEQ ID NO:19 (the pbm17 coding region) and nucleotides x_9 -1394 of SEQ ID NO:19, where x_9 is 66 or 114 (encoding the pbm17 extracellular domain); nucleotides 67-1839 of SEQ ID NO:21 (the pbmnew coding region) and nucleotides x_{10} -1434 of SEQ ID NO:21, where x_{10} is 67 or 115 (encoding the pbmnew extracellular domain); nucleotides 69-968 of SEQ ID NO:29 (the coding region of LIR-9 m1) and nucleotides x_{11} -854 of SEQ ID NO:29, where x_{11} is 69 or 170 (encoding the LIR-9 m1 extracellular domain); nucleotides 95-958 of SEQ ID NO:31 (the LIR-9 m2 coding region) and nucleotides x_{12} -844 of SEQ ID NO:31, where x_{12} is 95 or 200 (encoding the LIR-9 m2 extracellular domain); nucleotides x_{13} -912 of SEQ ID NO:33, where x_{13} is 115 or 216 (the LIR-9s1 coding region and extracellular region); nucleotides x_{14} -834 of SEQ ID NO:35, where x_{14} is 73 or 178 (the LIR-9s2 coding region and extracellular region); nucleotides 1-1350 of SEQ ID NO:37 (the LIR-10 coding region) and nucleotides 1-1179 of SEQ ID NO:37 (encoding all but a few amino-terminal amino acids of the LIR-10 extracellular domain).

Included in the present invention are DNAs encoding biologically active fragments of the LIR proteins whose amino

acid sequences are presented in SEQ ID NOS:2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38.

The present invention encompasses nucleotide sequences which, due to the degeneracy of the genetic code, encode polypeptides that are identical to polypeptides encoded by the nucleic acid sequences described above, and sequences complementary to them. Accordingly, within the present invention are DNA encoding biologically active LIR family members that include the coding region of a native human LIR family member cDNA, or fragments thereof, and DNA that is degenerate as a result of the genetic code to the native LIR polypeptide DNA sequence or the DNA of native LIR family members described herein.

In another aspect, the present invention includes LIR variants and derivatives as well as variants and derivatives of LIR family polypeptides, both recombinant and non-recombinant, that retain a desired biological activity. An LIR variant, as referred to herein, is a polypeptide substantially homologous to a native LIR polypeptide, as described herein, except the variant amino acid sequence differs from that of the native polypeptide because of one or more deletions, insertions or substitutions.

LIR family variants may be obtained from mutations of native LIR nucleotide sequences. Within the present invention are such DNA mutations or variants that include nucleotide sequences having one or more nucleotide additions, nucleotide deletions, or nucleotide substitutions compared to native DNA of LIR family members and that encode variant LIR polypeptides or variant LIR family members having a desired biological activity. Preferably the biological activity is substantially the same as that of the native LIR polypeptide.

Variant amino acid sequences and variant nucleotide sequences of the present invention preferably are at least 80% identical to that of a native LIR family member sequence. One method for determining the degree of homology or identity between a native amino acid or nucleotide sequence and a variant amino acid or nucleotide sequence is to compare the sequences using computer programs available for such purposes. One suitable computer program is the GAP program, version 6.0, described by Devereux et al. (*Nucl. Acids Res.* 12:387, 1984) and available from the University of Wisconsin Genetics Computer Group (UWGCG). The GAP program utilizes the alignment method of Needleman and Wunsch (*J. Mol. Biol.* 48:443, 1970), as revised by Smith and Waterman (*Adv. Appl. Math* 2:482, 1981). Briefly, the GAP program defines identity as the number of aligned symbols (i.e., nucleotides or amino acids) which are identical, divided by the total number of symbols in the shorter of the two sequences being compared. The preferred default parameters for the GAP program include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) for nucleotides, and the weighted comparison matrix of Gribskov and Burgess, *Nucl. Acids Res.* 14:6745, 1986, as described by Schwartz and Dayhoff, eds., *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, pp. 353-358, 1979; (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps.

Alterations of native LIR amino acid sequences may be provided by using any of a number of known techniques. As described above, mutations can be introduced at selected sequence sites by synthesizing oligonucleotides containing a mutant coding sequence, flanked by restriction sites enabling its ligation to fragments of the native sequence. After ligating the synthesized oligonucleotides to the native sequence fragments, the resulting reconstructed nucleotide sequence will encode an analog or variant polypeptide having the desired

amino acid insertion, substitution, or deletion. Another procedure suitable for preparing variant polypeptides is oligonucleotide-directed site-specific mutagenesis procedures which provide genes having specific codons altered in accordance with the desired substitution, deletion, or insertion. Techniques for making such alterations include those disclosed in the following references: Walder et al. *Gene*, 42:133, 1986; Bauer et al., *Gene* 37:73, 1985; Craik, *BioTechniques*, 12-19 January, 1985; Smith et al. *Genetic Engineering: Principles and Methods*, Plenum Press, 1981; and U.S. Pat. Nos. 4,518,584 and 4,737,462, all of which are incorporated herein by reference.

Variant polypeptides of the present invention may have amino acid sequences which are conservatively substituted, meaning that one or more amino acid residues of a native LIR polypeptide family member is replaced by different residues, such that the variant polypeptide retains a desired biological activity that is essentially equivalent to that of a native LIR family member. In general, a number of approaches to conservative substitutions are well known in the art and can be applied in preparing variant of the present invention. For example, amino acids of the native polypeptide sequence may be substituted for amino acids which do not alter the secondary and/or tertiary structure of the LIR polypeptide. Other suitable substitutions include those which involve amino acids outside of the ligand-binding domain of interest. One approach to conservative amino acid substitutions involves replacing one or amino acids with those having similar physicochemical characteristics, e.g. substituting one aliphatic residue for another such as Ile, Val, Leu, or Ala for one another; substituting one polar residue for another (such as between Lys and Arg; Glu and Asp; or Gln and Asn); or substituting entire regions having similar hydrophobicity or hydrophilic characteristics.

LIR polypeptide variants can be tested for binding to cells as described in Examples 5 and 6 and for phosphatase binding activity as described in Example 11 to confirm biological activity. Other LIR variants within the present invention include polypeptides which are altered by changing the nucleotide sequence encoding the polypeptide so that selected polypeptide Cys residues are deleted or replaced with one or more alternative amino acids. These LIR variants will not form intramolecular disulfide bridges upon renaturation. Naturally occurring LIR polypeptides selected for alteration by deleting or altering Cys residues preferably do not have biological activities which depend upon disulfide bridges formed by the Cys residue. Other possible variants are prepared by techniques which cause the modification of adjacent dibasic amino acid residues to enhance expression in yeast systems in which KEX2 protease activity is present. EP 212,914 discloses site-specific mutagenesis techniques for inactivating KEX2 protease processing sites in a protein. KEX2 protease processing sites are inactivated by deleting, adding or substituting residues to alter Arg-Arg, Arg-Lys, and Lys-Arg pairs to eliminate the occurrence of these adjacent basic residues. Lys-Lys and pairings are considerably less susceptible to KEX2 cleavage, and conversion of Arg-Lys or Lys-Arg to Lys-Lys represents a conservative and preferred approach to inactivating KEX2 sites.

Naturally occurring LIR variants are also encompassed by the present invention. Examples of such variants are proteins that result from alternative mRNA splicing events or from proteolytic cleavage of an LIR polypeptide. Alternative splicing of mRNA may yield a truncated but biologically active LIR polypeptide such as a naturally occurring soluble form of the protein. Variations attributable to proteolysis include difference in the N- or C-termini upon expression in different

types of host cells, due to proteolytic removal of one or more terminal amino acids from the LIR polypeptide. In addition, proteolytic cleavage may release a soluble form of LIR from a membrane-bound form of the polypeptide. Other naturally occurring LIR variations are those in which differences from the amino acid sequence of SEQ ID Nos: 2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38 are attributable to genetic polymorphism, the allelic variation among individuals.

Within the scope of the present invention are derivative LIR family polypeptides which include native or variant LIR polypeptides modified to form conjugates with selected chemical moieties. The conjugates can be formed by covalently linking another moiety to a native or variant LIR or by non-covalently linking another moiety to a native or variant LIR. Suitable chemical moieties include but are not limited to glycosyl groups, lipids, phosphates, acetyl groups, and other proteins or fragments thereof. Techniques for covalently linking chemical moieties to proteins are well known in the art and are generally suitable for preparing derivative LIR polypeptides. For example, active or activated functional groups on amino acid side chains can be used as reaction sites for covalently linking a chemical moiety to a LIR polypeptide. Similarly, the N-terminus or C-terminus can provide a reaction site for a chemical moiety. LIR polypeptides or fragments conjugated with other proteins or protein fragments can be prepared in recombinant culture as N-terminal or C-terminal fusion products. For example, the conjugate or fusion portions may include a signal or leader sequence attached to an LIR molecule at its N-terminus. The signal or leader peptide co-translationally or post-translationally directs transfer of the conjugate from its site of synthesis to a site inside or outside of the cell membrane.

One useful LIR polypeptide conjugate is one incorporating a poly-His or the antigenic identification peptides described in U.S. Pat. No. 5,011,912 and in Hopp et al., *Bio/Technology* 6:1124, 1988. For example, the FLAG® peptide, Asp-Tyr-Lys-Asp-Asp-Asp-Lys (SEQ ID NO:39) is highly antigenic and provides an epitope reversibly bound by a specific monoclonal antibody, thus enabling rapid assay and facile purification of expressed recombinant protein. This sequence is specifically cleaved by bovine mucosal enterokinase at the residue immediately following the Asp-Lys pairing. Fusion proteins capped with this peptide may be resistant to intracellular degradation in *E. coli*. Murine hybridoma designated 4E11 produced a monoclonal antibody that binds the peptide of SEQ ID NO:39 in the presence of certain divalent metal cations, and has been deposited with the American Type Culture Collection under accession no HB 9259. Expression systems useful for producing recombinant proteins fused to the FLAG® peptide, and monoclonal antibodies that bind the peptide and are useful in purifying the recombinant proteins, are available from Eastman Kodak Company, Scientific Imaging Systems, New Haven, Conn.

Particularly suitable LIR fusion proteins are those in which an LIR polypeptide is in the form of an oligomer. Oligomers may be formed by disulfide bonds between cysteine residues on more than one LIR polypeptide, or by noncovalent interactions between LIR polypeptide chains. In another approach, LIR oligomers can be formed by joining LIR polypeptides or fragment thereof via covalent or noncovalent interactions between peptide moieties fused to the LIR polypeptide. Suitable peptide moieties include peptide linkers or spacers, or peptides that have the property of promoting oligomerization. Leucine zippers and certain polypeptides derived from antibodies are among the peptides that can promote oligomerization of LIR polypeptides attached thereto.

Other LIR fusion proteins which promote oligomer formation are fusion proteins having heterologous polypeptides fused to various portions of antibody-derived polypeptides (including the Fc domain). Procedures for preparing such fusion proteins are described in Ashkenazi et al. *PNAS USA* 88:10535, 1991; Byrne et al. *Nature* 344:667, 1990, and Hollenbaugh and Aruffo *Current Protocols in Immunology*, Supplement 4, pages 10.19.1-10.19.11, 1992; all of which are incorporated herein by reference. Example 1 and Example 5 below describe methods for preparing UL18:Fc and P3G2:Fc fusion proteins, respectively, by fusing P3G2 and UL18 to an Fc region polypeptide derived from an antibody. This is accomplished by inserting into an expression vector a gene fusion encoding the P3G2:Fc fusion protein and expressing the P3G2:Fc fusion protein. The fusion proteins are allowed to assemble much like antibody molecules, whereupon inter-chain disulfide bonds form between the Fc polypeptides, yielding divalent P3G2 polypeptide. In a similar approach, P3G2 or any LIR polypeptide may be substituted for the variable portion of an antibody heavy or light chain. If fusion proteins are made with heavy and light chains of an antibody, it is possible to form a LIR oligomer with as many as four LIR regions.

Thus, the invention encompasses nucleic acids that encode fusion proteins that include the Fc region of Ig and an amino acid sequence including the extracellular region of any of the LIR family member proteins. Such extracellular regions include, e.g., amino acids x_1 -458 of SEQ ID NO:2, where x_1 is amino acids 1 or 17; amino acids x_2 -459 of SEQ ID NO:4, where x_2 is amino acid 1 or 17; amino acids x_3 -439 of SEQ ID NO:8, where x_3 is amino acid 1 or 17; amino acids x_4 -458 of SEQ ID NO:10, where x_4 is amino acid 1 or 17; amino acids x_5 to 261 of SEQ ID NO:12, wherein x_5 is amino acid 1 or 17; amino acids x_6 to 461 of SEQ ID NO:14, wherein x_6 is amino acid 1 or 17; amino acids x_7 -449 of SEQ ID NO:16, where x_7 is amino acid 1 or 17; amino acids x_8 -259 of SEQ ID NO:18, where x_8 is amino acid 1 or 17; amino acids x_9 -443 of SEQ ID NO:20, where x_9 is amino acid 1 or 17; amino acids x_{10} to 456 of SEQ ID NO:22, wherein x_{10} is amino acid 1 or 17; amino acids x_{11} to 262 of SEQ ID NO:30, wherein x_{11} is amino acid 1 or 35; amino acids x_{12} to 250 of SEQ ID NO:32, wherein x_{12} is amino acid 1 or 36; amino acids x_{13} to 265 of SEQ ID NO:34, wherein x_{13} is amino acid 1 or 35; and amino acids x_{14} to 253 of SEQ ID NO:36, wherein x_{14} is amino acid 1 or 36; and amino acids 1-393 of SEQ ID NO:38.

As used herein, a Fc polypeptide includes native and mutein forms, as well as truncated Fc polypeptides containing the hinge region that promotes dimerization. One suitable Fc polypeptide is the native Fc region polypeptide derived from a human IgG1, which is described in PCT application WO 93/10151, hereby incorporated herein by reference. Another useful Fc polypeptide is the Fc mutein described in U.S. Pat. No. 5,457,035. The amino acid sequence of the mutein is identical to that of the native Fc sequence presented in WO 93/10151, except that amino acid 19 has been changed from Leu to Ala, amino acid 20 has been changed from Leu to Glu, and amino acid 22 has been changed from Gly to Ala. This mutein Fc exhibits reduced affinity for immunoglobulin receptors.

Alternatively, oligomeric LIR polypeptide variants may include two or more LIR peptides joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627, incorporated herein by reference. Fusion proteins which include multiple LIR polypeptides separated by peptide linkers may be produced conventional recombinant DNA technology.

Another method for preparing oligomeric LIR polypeptide variants involves use of a leucine zipper. Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found. Leucine zippers were first identified in several DNA-binding proteins (Landschulz et al. *Science* 240:1759, 1988). Among the known leucine zippers are naturally occurring peptides and peptide derivatives that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric LIR polypeptides or oligomeric polypeptides of the LIR family are those described in PCT application WO 94/10308, incorporated herein by reference. Recombinant fusion proteins having a soluble LIR polypeptide fused to a peptide that dimerizes or trimerizes in solution may be expressed in suitable host cells, and the resulting soluble oligomeric LIR polypeptide recovered from the culture supernatant.

Numerous reagents useful for cross-linking one protein molecule to another are known. Heterobifunctional and homobifunctional linkers are available for this purpose from Pierce Chemical Company, Rockford, Ill., for example. Such linkers contain two functional groups (e.g., esters and/or maleimides) that will react with certain functional groups on amino acid side chains, thus linking one polypeptide to another.

One type of peptide linker that may be employed in the present invention separates polypeptide domains by a distance sufficient to ensure that each domain properly folds into the secondary and tertiary structures necessary for the desired biological activity. The linker also should allow the extracellular portion to assume the proper spatial orientation to form the binding sites for ligands.

Suitable peptide linkers are known in the art, and may be employed according to conventional techniques. Among the suitable peptide linkers are those described in U.S. Pat. Nos. 4,751,180 and 4,935,233, which are hereby incorporated by reference. A peptide linker may be attached to LIR polypeptides by any of the conventional procedures used to attach one polypeptide to another. The cross-linking reagents available from Pierce Chemical Company as described above are among those that may be employed. Amino acids having side chains reactive with such reagents may be included in the peptide linker, e.g., at the termini thereof. Preferably, a fusion proteins formed via a peptide linker are prepared by recombinant DNA technology.

The fusion proteins of the present invention include constructs in which the C-terminal portion of one protein is fused to the linker which is fused to the N-terminal portion of another protein. Peptides linked in such a manner produce a single protein which retains the desired biological activities. The components of the fusion protein are listed in their order of occurrence (i.e., the N-terminal polypeptide is listed first, followed by the linker and then the C-terminal polypeptide).

A DNA sequence encoding a fusion protein is constructed using recombinant DNA techniques to insert separate DNA fragments encoding the desired proteins into an appropriate expression vector. The 3' end of a DNA fragment encoding one protein is ligated (via the linker) to the 5' end of the DNA fragment encoding another protein with the reading frames of the sequences in phase to permit translation of the mRNA into a single biologically active fusion protein. A DNA sequence encoding an N-terminal signal sequence may be retained on the DNA sequence encoding the N-terminal polypeptide, while stop codons, which would prevent read-through to the second (C-terminal) DNA sequence, are eliminated. Conversely, a stop codon required to end translation is retained on

the second DNA sequence. DNA encoding a signal sequence is preferably removed from the DNA sequence encoding the C-terminal polypeptide.

A DNA sequence encoding a desired polypeptide linker may be inserted between, and in the same reading frame as, the DNA sequences encoding the two proteins using any suitable conventional technique. For example, a chemically synthesized oligonucleotide encoding the linker and containing appropriate restriction endonuclease cleavage sites may be ligated between the sequences encoding Fc and a P3G2 polypeptide.

Within the scope of the present invention are recombinant expression vectors for expressing polypeptides of the LIR family, and host cells transformed with the expression vectors. Expression vectors of the invention include DNA that encodes a LIR family member operably linked to suitable transcriptional or translational regulatory nucleotide sequences, such as those derived from a mammalian, microbial, viral, or insect gene. Examples of regulatory sequences include transcriptional promoters, operators, or enhancers, an mRNA ribosomal binding site, and appropriate sequences which control transcription and translation initiation and termination. Nucleotide sequences are operably linked when the regulatory sequence functionally relates to the LIR DNA sequence. Thus, a promoter nucleotide sequence is operably linked to a LIR DNA sequence if the promoter nucleotide sequence controls the transcription of the LIR DNA sequence. An origin of replication that confers the ability to replicate in the desired host cells, and a selection gene by which transformants are identified, are generally incorporated in the expression vector.

In addition, a sequence encoding an appropriate signal peptide can be incorporated into expression vectors. A DNA sequence for a signal peptide (secretory leader) may be fused in frame to the LIR sequence so that the LIR is initially translated as a fusion protein comprising the signal peptide. A signal peptide that is functional in the intended host cells promotes extracellular secretion of the LIR polypeptide. The signal peptide is cleaved from the LIR polypeptide upon secretion of the LIR polypeptide from the cell.

The recombinant expression vectors of the present invention may include any DNA encoding a LIR polypeptide. Exemplary DNAs for inclusion in such expression vectors include the nucleic acid molecules whose sequences are shown in SEQ ID NOS:1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 29, 31, 33, 35 and 37.

Suitable host cells for expression of LIR polypeptides include prokaryotes, yeast or higher eukaryotic cells. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described, for example, in Pouwels et al. *Cloning Vectors: A Laboratory Manual*, Elsevier, New York, (1985). Cell-free translation systems could also be employed to produce P3G2 polypeptides using RNAs derived from DNA constructs disclosed herein.

Prokaryote host cells suitable in the practice of the present invention include gram negative or gram positive organisms, for example, *E. coli* or Bacilli. Suitable prokaryotic host cells for transformation include, for example, *E. coli*, *Bacillus subtilis*, *Salmonella typhimurium*, and various other species such as *Pseudomonas*, *Streptomyces*, and *Staphylococcus*. In a prokaryotic host cell, such as *E. coli*, a P3G2 polypeptide may include an N-terminal methionine residue to facilitate expression of the recombinant polypeptide. The N-terminal Met may be cleaved from the expressed recombinant LIR polypeptide.

Expression vectors for use in prokaryotic host cells generally include one or more phenotypic selectable marker genes. A phenotypic selectable marker gene is, for example, a gene encoding a protein that confers antibiotic resistance or that supplies an autotrophic requirement. Examples of useful expression vectors for prokaryotic host cells include those derived from commercially available plasmids such as the cloning vector pBR322 (ATCC 37017). pBR322 contains genes for ampicillin and tetracycline resistance and thus provides simple means for identifying transformed cells. An appropriate promoter and a LIR family DNA may be inserted into the pBR322 vector. Other commercially available vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and pGEM1 (Promega Biotec, Madison, Wis., USA).

Promoter sequences commonly used for recombinant prokaryotic host cell expression vectors include β -lactamase (penicillinase), lactose promoter system (Chang et al. *Nature* 75:615, 1978; and Goeddel et al., *Nature* 281:544, 1979), tryptophan (trp) promoter system (Goeddel et al., *Nucl. Acids Res.* 8:4057, 1980); and EP-A-36776) and tac promoter (Maniatis, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, p. 412, 1982). A particularly useful prokaryotic host cell expression system employs a phase λ P_L promoter and a cI857ts thermolabile repressor sequence. Plasmid vectors available from the American Type Culture Collection which incorporate derivatives of the λ P_L promoter include plasmid pHUB2 (resident in *E. coli* strain JMB9, ATCC 37092) and pPLc28 (resident in *E. coli* RR1, ATCC 53082).

Alternatively, LIR polypeptides may be expressed in yeast host cells, preferably from the *Saccharomyces* genus (e.g., *S. cerevisiae*). Other genera of yeast, such as *Pichia* or *Kluyveromyces* may also be employed. Yeast vectors will often contain an origin of replication sequence from a 2 μ yeast plasmid, an autonomously replicating sequence (ARS), a promoter region, sequences for polyadenylation, sequences for transcription termination, and a selectable marker gene. Suitable promoter sequences for yeast vectors include, among others, promoters for metallothionein, 3-phosphoglycerate kinase (Hitzeman et al., *J. Biol. Chem.* 255:2073, 1980) or other glycolytic enzymes (Hess et al., *J. Adv. Enzyme Reg.* 7:149, 1968); and Holland et al., *Biochem.* 17:4900, 1978), such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phospho-glucose isomerase, and glucokinase. Other suitable vectors and promoters for use in yeast expression are further described in Hitzeman, EPA-73,675. Another alternative is the glucose-repressible ADH2 promoter described by Russell et al. (*J. Biol. Chem.* 258:2674, 1982) and Beier et al. (*Nature* 300:724, 1982). Shuttle vectors replicable in both yeast and *E. coli* may be constructed by inserting DNA from pBR322 for selection and replication in *E. coli* (Amp^r gene and origin of replication) into the above-described yeast vectors.

The yeast α -factor leader sequence may be employed to direct secretion of the LIR polypeptide. The α -factor leader sequence is often inserted between the promoter sequence and the structural gene sequence. See, e.g., Kurjan et al., *Cell* 30:933, 1982 and Bitter et al., *Proc. Natl. Acad. Sci. USA* 81:5330, 1984. Other leader sequences suitable for facilitating secretion of recombinant polypeptides from yeast hosts are known to those of skill in the art. A leader sequence may

be modified near its 3' end to contain one or more restriction sites. This will facilitate fusion of the leader sequence to the structural gene.

Yeast transformation protocols are known to those of skill in the art. One such protocol is described by Hinnen et al., *Proc. Natl. Acad. Sci. USA* 75:1929, 1978. The Hinnen et al. protocol selects for Trp⁺ transformants in a selective medium, wherein the selective medium consists of 0.67% yeast nitrogen base, 0.5% casamino acids, 2% glucose, 10 μ g/mL adenine and 20 μ g/mL uracil.

Yeast host cells transformed by vectors containing an ADH2 promoter sequence may be grown for inducing expression in a "rich" medium. An example of a rich medium is one having 1% yeast extract, 2% peptone, and 1% glucose supplemented with 80 μ g/mL uracil. Derepression of the ADH2 promoter occurs when glucose is exhausted from the medium.

Mammalian or insect host cell culture systems may be used to express recombinant LIR polypeptides. Baculovirus systems for production of heterologous proteins in insect cells are reviewed by Luckow and Summers, *Bio/Technology* 6:47 (1988). Established cell lines of mammalian origin also may be employed. Examples of suitable mammalian host cell lines include the COS-7 line of monkey kidney cells (ATCC CRL 1651)(Gluzman et al., *Cell* 23:175, 1981), L cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells, HeLa cells, and BHK (ATCC CRL 10) cell lines, and the CVI/EBNA cell cline derived from the African green monkey cell line CVI (ATCC CCL 70) as described by McMahan et al. (*EMBO J.* 10:2821, 1991). COS-1 (ATCC CRL-1650).

Transcriptional and translational control sequences for mammalian host cell expression vectors may be excised from viral genomes. Commonly used promoter sequences and enhancer sequences are derived from Polyoma virus, Adenovirus 2, Simian Virus 40 (SV40), and human cytomegalovirus. DNA derived from the SV40 viral genome, for example, SV40 origin, early and late promoter, enhancer, splice, and polyadenylation sites may be used to provide other genetic elements for expression of a structural gene sequence in a mammalian host cell. Viral early and late promoters are particularly useful because both are easily obtained from a viral genome as a fragment which may also contain a viral origin of replication (Fiers et al., *Nature* 273:113, 1978). Smaller or larger SV40 fragments may also be used, provided the approximately 250 by sequence extending from the HIND III site toward the BglI site located in the SV40 viral origin of replication site is included.

Suitable expression vectors for use in mammalian host cells can be constructed as disclosed by Okayama and Berg (*Mol. Cell. Biol.* 3:280, 1983). One useful system for stable high level expression of mammalian receptor cDNAs in C127 murine mammary epithelial cells can be constructed substantially as described by Cosman et al. (*Mol. Immunol.* 23:935, 1986). A high expression vector, PMLSV N1/N4, described by Cosman et al., *Nature* 312:768, 1984 has been deposited as ATCC 39890. Additional mammalian expression vectors are described in EP-A-0367566, and in WO 91/18982. Still additional expression vectors for use in mammalian host cells include pDC201 (Sims et al., *Science* 241:585, 1988), pDC302 (Mosley et al. *Cell* 59:335, 1989), and pDC406 (McMahan et al., *EMBO J.* 10:2821, 1991). Vectors derived from retroviruses also may be employed. One preferred expression system employs pDC409 as discussed in Example 5 below.

For expression of LIR polypeptides the expression vector may comprise DNA encoding a signal or leader peptide. In

place of the native signal sequence, a heterologous signal sequence may be added, such as the signal sequence for interleukin-7 (IL-7) described in U.S. Pat. No. 4,965,195; the signal sequence for interleukin-2 receptor described in Cosman et al., *Nature* 312:768, 1984); the interleukin-4 signal peptide described in EP 367,566; the type I interleukin-1 receptor signal peptide described in U.S. Pat. No. 4,968,607; and the type II interleukin-1 receptor signal peptide described in EP 460,846.

Further contemplated within the present invention are purified LIR family polypeptides, and processes for their purification. The purified polypeptides of the present invention may be purified from the above-described recombinant expression systems or may be purified from naturally occurring cells. The desired degree of purity may depend on the intended use of the protein with a relatively high degree of purity preferred when the protein is intended for in vivo use. Preferably, LIR polypeptide purification processes are such that no protein bands corresponding to proteins other than the desired LIR protein are detectable by SDS-polyacrylamide gel electrophoresis (SDS-PAGE). It will be recognized by one skilled in the art that multiple bands corresponding to any LIR polypeptide may be detected by SDS-PAGE, due to differential glycosylation, variations in post-translational processing, and the like, as discussed above. Most preferably, any specific LIR polypeptide is purified to substantial homogeneity, as indicated by a single protein band upon analysis by SDS-PAGE. The protein band may be visualized by silver staining, Coomassie blue staining, or by autoradiography or fluorescence if the protein is appropriately labeled.

One process for providing purified LIR polypeptides includes first culturing a host cell transformed with an expression vector comprising a DNA sequence that encodes the desired polypeptide under conditions that promote expressing the desired LIR polypeptide and then recovering the LIR polypeptide. As the skilled artisan will recognize, procedures for recovering the polypeptide will vary according to such factors as the type of host cells employed and whether the polypeptide is secreted in the culture medium is extracted from cells.

When the expression system secretes the polypeptide into the culture medium, the medium may be first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. Following the concentration step, the concentrate can be applied to a suitable purification matrix such as a gel filtration medium. Alternatively, an anion exchange resin can be employed, such as a resin matrix or resin substrate having pendant diethylaminoethyl (DEAE) groups. The matrices can be acrylamide, agarose, dextran, cellulose or other types commonly employed in protein purification. Similarly, a purification matrix having cation exchange groups such as sulfopropyl or carboxymethyl functionalities on an insoluble matrix can be used. Sulfopropyl groups are preferred. Still other purification matrices and methods suitable for providing purified LIR are high performance liquid chromatography using hydrophobic reversed phase media (RP-HPLC). One skilled in the art will recognize the any or all of the foregoing purification steps, in various combinations, can be employed to provide a purified LIR polypeptide.

Alternatively, LIR polypeptides can be purified by immunoaffinity chromatography. An affinity column containing an antibody that binds a LIR polypeptide may be prepared by conventional procedures and employed in purifying LIR. Example 5 describes a procedures for generating monoclonal antibodies directed against P3G2 which may be utilized in immunoaffinity chromatography.

Recombinant protein produced in bacterial culture may be isolated by first disrupting the host cells by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents and then extracting the polypeptide from cell pellets if the polypeptide is insoluble, or from the supernatant fluid if the polypeptide is soluble. After the initial isolation step, the purification process may include one or more concentrating, salting out, ion exchange, affinity, or size exclusion chromatography purification steps. For many application a final RP-HPLC purification step is beneficial.

Additional methods for providing LIR polypeptides and purified LIR polypeptides involves fermenting yeast which express proteins as a secreted protein. Secreted recombinant protein resulting from a large-scale fermentation can be purified by methods analogous to those disclosed by Urdal et al. (*J. Chromatog.* 296:171, 1984), involving two sequential, reversed-phase HPLC steps for purification of a recombinant protein on a preparative HPLC column.

LIR-P3G2 DNA in pDC406 vector was deposited with the American Type Culture Collection on Apr. 22, 1997 and assigned accession No. 97995. The deposit was made under the terms of the Budapest Treaty.

As described above and shown in Examples 6 and 14, LIR-P3G2 and LIR-pbm8 are MHC class I receptor molecules found on the surface of certain monocytes, B cells, and NK cells. With respect to monocytes, the expression of LIRs that are MHC class I binding proteins suggests that there is some requirement for monocytes to recognize MHC class I molecules. LIR-P3G2, LIR-pbm8 LIR and certain additional LIR family members contain cytoplasmic ITIM motifs. By analogy with the structure and function of known MHC class I receptor molecules, these LIRs are inhibitory receptors mediating negative signaling. Indeed, the results demonstrated in Example 11 reveal that LIRs associate with SHP-1 and inhibit FcR-mediated activation events. Thus, monocytes may express class I receptors in order to suppress cell-mediated lytic mechanisms. Monocytes rapidly phagocytose extracellular pathogens via FcR and, monocyte-FcR engagement induces propagation of immune responses by producing more systemic mediators, particularly TNF- α , IL-6 and IL-8. Thus, the LIRs play a role in monocyte and macrophage regulation of cytolytic and inflammatory responses against self tissues. The interplay between the FcR activatory signals and LIR inhibitory signal may allow low levels of self-reactive IgG to exist in circulation and bind to the monocyte membrane with initiating an immune response. For example, the expression of these inhibitory receptors can protect the developing embryo from maternal antibody-mediated allogeneic recognition.

With respect to LIRs on cells of the DC lineage, as described in Example 13 CD33⁺CD14⁻CD16⁻HLA⁻DR⁺DC co-express LIR-P3G2 and LIR-pbm8. It is suggested the DC FcR play a role in binding immune complexes and triggering DC activation signal following binding. Thus, LIRs expressed on DC may suppress DC activation through interactions of FcR.

Many LIR family members lack the ITIM motif and by analogy with the structure and function of known MHC class I receptors lacking ITIMs are activatory receptors. Failure of a receptor that mediates negative signaling could result in autoimmune diseases. Thus, engaging an LIR family member having ITIM motifs with an agonistic antibody or ligand can be used to downregulate a cell function in disease states in which the immune system is overactive and excessive inflammation or immunopathology is present. On the other hand, using an antagonistic antibody specific to the ITIM possess-

ing LIR receptor or a soluble form of the receptor can be used to block the interaction of the cell surface receptor with the receptor's ligand to activate the specific immune function in disease states associated with suppressed immune function. Since receptors lacking the ITIM motif send activatory signals once engaged as described above, failure of a receptor that mediates an activatory signal could result in suppressed immune function. Engaging the receptor with its agonistic antibody or ligand can be used to treat diseases associated with the suppressed immune function. Using an antagonistic antibody specific to the activatory LIR receptor or a soluble form of the receptor can be used to block the interaction of the activatory receptor with the receptor's ligand to down-regulate the activatory signaling.

Since LIR-P3G2 binds to various cells, LIR-P3G2 may be used to purify or isolate these cells from heterogeneous preparations. Additionally, P3G2 probes can be used to isolate and identify related molecules.

LIR polypeptides of the present invention may be used in developing treatments for any disorder mediated directly or indirectly by defective or insufficient amounts of any of the LIR polypeptides. A therapeutically effective amount of purified LIR protein is administered by a patient afflicted with such a disorder. Alternatively, LIR DNA may be employed in developing a gene therapy approach to treating such disorders. Disclosure herein of native LIR nucleotide sequence permits the detection of defective LIR genes, and the replacement thereof with normal LIR-encoding genes. Defective genes may be detected in vitro diagnostic assays, and by comparison of the native LIR nucleotide sequence disclosed herein with that of an LIR gene derived from a person suspected of harboring a defect in the gene.

The present invention also provides pharmaceutical compositions which may include an LIR polypeptide, or fragments or variants thereof with a physiologically acceptable carrier or diluent. Such carriers and diluents will be nontoxic to recipients at the dosages and concentrations employed. Such compositions may further include buffers, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) polypeptides, proteins, amino acids, carbohydrates including glucose, sucrose or dextrans, chelating agents such as EDTA, glutathione and other stabilizers and excipients commonly used in pharmaceutical compositions. The pharmaceutical compositions of the present invention may be formulated as a lyophilizate using appropriate excipient solutions as diluents. The pharmaceutical compositions may include an LIR polypeptide in any for described herein, including but not limited to active variants, fragments, and oligomers. LIR polypeptides may be formulated according to known methods that are used to prepare pharmaceutically useful compositions. Components that are commonly employed in pharmaceutical formulations include those described in *Remington's Pharmaceutical Sciences*, 16th ed. (Mack Publishing Company, Easton, Pa., 1980).

The pharmaceutical preparations of the present invention may be administered to a patient, preferably a human, in a manner appropriate to the indication. Thus, for example, the compositions can be administered by intravenous injection, local administration, continuous infusion, sustained release from implants, etc. Appropriate dosages and the frequency of administration will depend on such factors as the nature and severity of the indication being treated, the desired response, the condition of the patient and so forth.

In preferred embodiments an LIR polypeptide used in the pharmaceutical compositions of the present invention is purified such that the LIR polypeptide is substantially free of other proteins of natural or endogenous origin, desirably con-

taining less than about 1% by mass of protein contaminants residual of the production processes. Such compositions, however, can contain other proteins added as stabilizers, carriers, excipients or co-therapeutics.

LIR encoding DNAs and DNA fragments disclosed herein find use in the production of LIR polypeptides, as described above. In one embodiment, such fragments comprise at least about 17 consecutive nucleotides, more preferably at least 30 consecutive nucleotides, of LIR DNA. DNA and RNA complements of the fragments have similar utility. Among the uses of LIR nucleic acid fragments are as probes or primers in polymerase chain reactions. For example, a probe corresponding to a fragment of DNA encoding the extracellular domain of LIR may be employed to detect the presence of LIR nucleic acids in vitro assays and in other probing assays such as Northern Blot and Southern blot assays. Cell types expressing an LIR polypeptide can be identified using LIR family nucleic acid probes using probing procedures well known in the art. Those skilled in the art have the knowledge to choose a probe of suitable length and apply conventional PCR techniques to isolate and amplify a DNA sequence.

Nucleic acid fragments may also be used as a probe in cross species hybridization procedures to isolate LIR DNA from other mammalian species. As one example, a probe corresponding to the extracellular domain of an LIR polypeptide may be employed. The probes may be labeled (e.g., with ^{32}P) by conventional techniques.

Other useful fragments of LIR nucleic acids are sense or antisense oligonucleotides, which may comprise either RNA or DNA, and which correspond in sequence to an LIR mRNA (sense), to the complement of an LIR mRNA (antisense), or to the non-coding strand of a double-stranded LIR DNA, such as P3G2 DNA (antisense). Thus, an antisense oligonucleotide will form a hybrid duplex with an mRNA sequence. Such oligonucleotides generally are at least 14 nucleotides, and preferably are from about 14 to about 30 nucleotides. The ability to create an antisense or a sense oligonucleotide based upon a cDNA sequence for a given protein is described in, for example, Stein and Cohen, *Cancer Res.* 48:2659, 1988 and van der Krol et al., *BioTechniques* 6:958, 1988.

Binding antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block translation (RNA) or transcription (DNA) by one of several means, including enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means. These oligonucleotides thus may be used to block LIR expression.

In one embodiment antisense or sense LIR oligonucleotides used in binding procedures may encompass oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Oligonucleotides having sugar linkages resistant to endogenous nucleases are stable in vivo (i.e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences. Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10448, and other moieties that increase affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-(L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

Antisense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example, CaPO₄-mediated DNA transfection, electroporation, or by using gene transfer vectors such as Epstein-Barr virus. Antisense or sense oligonucleotides are preferably introduced into a cell containing the target nucleic acid sequence by inserting the antisense or sense oligonucleotide into a suitable retroviral vector, then contacting the cell with the retroviral vector containing the inserted sequence, either in vivo or ex vivo. Suitable retroviral vectors include, but are not limited to, those derived from the murine retrovirus M-MuLV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated DCT5A, DCT5B and DCT5C (see PCT Application US 90/02656).

Sense or antisense oligonucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugating the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind its corresponding molecule or receptor, or block entry of the sense of antisense oligonucleotide or its conjugated version into the cell.

Alternatively, a sense or an antisense oligonucleotide may be introduced into a cell containing the target nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

In still a further aspect, the present invention provides antibodies that specifically bind LIR polypeptides, i.e., antibodies bind to LIR polypeptides via an antigen-binding site of the antibody (as opposed to non-specific binding). Antibodies of the present invention may be generated using LIR polypeptides or immunogenic fragments thereof. Polyclonal and monoclonal antibodies may be prepared by conventional techniques. See, for example, *Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses*, Kennet et al. (eds.), Plenum Press, New York 1980; and *Antibodies: A Laboratory Manual*, Harlow and Land (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1988. An exemplary procedure for producing monoclonal antibodies immunoreactive with P3G2-LIR is further illustrated in Example 5 below.

Included within the scope of the present invention are antigen binding fragments of antibodies which specifically bind to an LIR polypeptide. Such fragments include, but are not limited to, Fab, F(ab'), and F(ab')₂. Antibody variants and derivatives produced by genetic engineering techniques are contemplated as within the presented invention.

The monoclonal antibodies of the present invention include chimeric antibodies, e.g., humanized versions of murine monoclonal antibodies. Such antibodies may be prepared by known techniques and offer the advantage of reduced immunogenicity when the antibodies are administered to humans. In one embodiment a humanized monoclonal antibody comprises the variable region of a murine antibody (or just the antigen binding site thereof) and a constant region derived from a human antibody. Alternatively, a humanized antibody fragment may comprise the antigen binding site of a murine monoclonal antibody and a variable region fragment (lacking the antigen-binding site) derived from a human antibody. Procedures for the production of chimeric and further engineered monoclonal antibodies

include those described in Riechmann et al., *Nature* 332:232, 1988; Lie et al. *PNAS* 84:3439, 1987; Larrick et al. *Bio/Technology* 7:934, 1989; and Winter and Harris *TIPS* 14:139, 1993.

As mentioned above, antibodies of the present invention are useful in vitro or in vivo assays to detect the presence of LIR polypeptides and in purifying an LIR polypeptide by affinity chromatography.

Additionally, antibodies capable of blocking an LIR from binding to target cells may be used to inhibit a biological activity of an LIR polypeptide. More specifically, therapeutic compositions of an antibody antagonistic to one or more LIR family members having the ITIM motif may be administered to an individual in order to block the interaction of a cell surface LIR with its ligand. The result is an activation of immune function and is particularly beneficial in disease states in which the immune system is hyporesponsive or suppressed. Conversely, therapeutic compositions of an antibody antagonistic to one or more LIR family members lacking the ITIM motif may be used to obtain the opposite effect and be beneficial in disease states in which the immune system is overactive and excessive inflammation or immunopathology is present.

Pharmaceutical compositions which include at least one antibody that is immunoreactive with an LIR polypeptide and a suitable diluent, excipient, or carrier, are considered with the present invention. Suitable diluents, excipients, and carriers are described in the context of pharmaceutical compositions which include polypeptides of the present invention.

The following examples are provided to illustrate certain embodiments of the invention, and are not to be construed as limiting the scope of the invention.

EXAMPLES

Example 1

Isolating and Expressing Viral Protein

DNA encoding P3G2 polypeptide of the present invention was identified by isolating and expressing a viral glycoprotein, UL18, known to be expressed on cells infected with HCMV, and then expressing and using a UL18/Fc fusion protein to search for UL18 receptors. DNA encoding UL18 and its amino acid sequence are known and described in Beck, S., B. G. Barrell, *Nature* 331:269-272, 1988. The following describes isolating UL18 and preparing the UL18/Fc fusion protein.

Using standard techniques, total RNA was isolated from Human Foreskin Fibroblasts infected with HCMV (AD169) at three different transcription stages-immediate early (IE, 8 p.i.h.), early (24 p.i.h.) and late (48 p.i.h.). Because UL18 is known to be transcribed early in the infection, the IE total RNA was polyA⁺ selected and used to construct an HCMV-IE cDNA library using a cDNA kit according to the manufacturer's instructions (Pharmacia TIME SAVER cDNA Kit). In order to isolate the full length UL18 gene, two oligonucleotide primers known to include the terminal sequences of the UL18 gene were synthesized and used to isolate and amplify the UL18 gene from the HCMV-IE cDNA library. The primers had the following sequences and included Not I restriction sites which incorporate into the PCR product:

(SEQ ID NO: 23)
 Not I
 5' - TAT GCG GCC GCC ATG ATG ACA ATG TGG T - 3'

(SEQ ID NO: 24)
 5' - TAT GCG GCC GCC CCT TGC GAT AGC G - 3'
 Not I

The PCR conditions included one 5 minute 95° C. cycle followed by 30 cycles of 45 seconds at 95°, 45 seconds at 58° and 45 seconds at 72°, and then one cycle for 5 minutes at 72° C. The PCR product was electrophoresed on a 1% agarose gel and sized using ethidium bromide to visualize the separated DNA products. The presence of DNA of having the expected size of approximately 1.1 kb was confirmed.

The pDC409 expression vector, a vector derived from pDC406 (McMahan et al., *EMBO J.* 10:2821, 1991) but having a single Bgl II site was selected for the cloning process. The PCR product was subcloned into a pDC409 expression vector through the Not I sites, sequenced and the amino acid sequence deduced from the DNA sequence. The determined nucleotide sequence and amino acid sequence were identical to the previously published sequences (*ibid.*).

A fusion protein of the extracellular region of UL18 and a mutein human IgG1 Fc region (UL18:Fc) was prepared by first isolating cDNA encoding the extracellular region of UL18 using primers which flank the extracellular region of UL18. The primers were synthesized with Sal I and Bgl II restriction sites inserted at the 5' and 3' termini so that the PCR amplified cDNA introduced Sal I and Bgl II restriction sites at the 5' and 3' ends, respectively. The primers had the following sequences:

(SEQ ID NO: 25)
 5' - ATA GTC GAC AAC GCC ATG ATG ACA ATG TGG
 Sal I
 TG - 3'

(SEQ ID NO: 26)
 5' - TAA AGA TCT GGG CTC GTT AGC TGT CGG GT - 3'
 Bgl II

The conditions for the PCR reaction were as described above except that the template was the full length gene isolated as just described.

To prepare a vector construct for expressing fusion protein, sUL18:Fc, for use in cell binding studies, a DNA fragment encoding the Fc region of a human IgG1 antibody was isolated from a plasmid using Bgl II and Not I restriction enzymes. The encoded Fc portion was the mutein Fc described in U.S. Pat. No. 5,457,035 having reduced affinity for immunoglobulin receptors. The Bgl II site on the sUL18 gene was used to ligate the sUL18 gene DNA to the Bgl II site on the Fc gene to form a sUL18:Fc fusion DNA construction having an N-terminal Sal I restriction site and a C-terminal Not I restriction site. This fusion sUL18:Fc DNA construct was then ligated into pDC409 expression vector at its Sal I and Not I sites to form a 409/sUL18:Fc DNA construct.

The monkey cell line COS-1 (ATCC CRL-1650) was used to confirm expression of the fusion protein. COS-1 cells in 6-well plates (2x10⁵ cells per well) were transfected with about 2 µg of the DNA construct 409/sUL18:Fc per well. The cells were cultured for 2-3 days in 5% FBS/DMEM/F12 (available from GIBCO), then washed twice with PBS, starved for 1 hour in cysteine/methionine depleted RPMI (available from GIBCO as RPMI 1640) and metabolically

labeled with 100 µCi/mL of ³⁵S-Met/Cys for 4 hours. The supernatant was spun clear to remove loose cells and 150 µL of the supernatant was incubated with 100 µL of RIPA (0.05% Tween 20, 0.1% SDS, 1% Triton X-100, 0.5% deoxycholate in PBS) buffer and 50 µL of 50% Protein A-Sepharose solid support beads at 4° C. for 1 hour. Protein A-Sepharose is a Sepharose solid support (available from Pharmacia) having immobilized Protein A which binds the Fc portion of the fusion protein. After washing the solid support with RIPA to remove unbound material, fusion protein bound to the Protein A-Sepharose solid support was eluted from the Protein A-Sepharose using 35 µL of SDS-PAGE reducing sample buffer and then heated at 100° C. for 5 minutes. The eluant was then electrophoresed on a 4-20% SDS polyacrylamide gradient gel with ¹⁴C labeled protein molecular weight markers. After electrophoresis the gel was fixed with 8% acetic acid and enhanced at room temperature for 20 minutes with Amplifier available from Amersham. After drying the gel under vacuum it was exposed to x-ray film. Film analysis confirmed that the expected protein, a 100-120 kDa protein which includes the mutein Fc region of IgG and UL18 extracellular domains fused to the Fc, was expressed.

Once cells expressing the fusion protein were identified large scale cultures of transfected cells were grown to accumulate supernatant from cells expressing the fusion protein. This procedure involved transfecting COS-1 cells in T175 flasks with 15 µg of the UL18/Fc/409 fusion DNA per flask. After 7 days of culture in medium containing 0.5% low immunoglobulin bovine serum, a solution of 0.2% azide was added to the supernatant and the supernatant was filtered through a 0.22 µm filter. Then approximately 1 L of culture supernatant was passed through a BioCad Protein A HPLC protein purification system using a 4.6x100 mm Protein A column (POROS 20A from PerSeptive Biosystems) at 10 mL/min. The Protein A column binds the Fc portion of the sUL18/Fc fusion protein in the supernatant, immobilizing the fusion protein and allowing other components of the supernatant to pass through the column. The column was washed with 30 mL of PBS solution and bound sUL18/Fc was eluted from the HPLC column with citric acid adjusted to pH 3.0. Eluted purified sUL18/Fc was neutralized as it eluted using 1M Hepes solution at pH 7.4. The pooled eluted protein was analyzed using SDS PAGE with silver staining, confirming expression of the 100-120 kDa UL18/Fc fusion protein.

Example 2

Screening Cell Lines for Binding to UL18

The sUL18/Fc protein isolated as described in Example 1 was used to screen cells lines to which it binds using quantitative binding studies according to standard flow cytometry methodologies. For each cell line screened, the procedure involved incubating approximately 100,000 of the cells blocked with 2% FCS (fetal calf serum), 5% normal goat serum and 5% rabbit serum in PBS for 1 hour. Then the blocked cells were incubated with 5 µg/mL of sUL18/Fc fusion protein in 2% FCS, 5% goat serum and 5% rabbit serum in PBS. Following the incubation the sample was washed 2 times with FACS buffer (2% FCS in PBS) and then treated with mouse anti human Fc/biotin (purchased from Jackson Research) and SAPE (streptavidin-phycoerythrin purchased from Molecular Probes). This treatment causes the anti human Fc/biotin to bind to any bound sUL18/Fc and the SAPE to bind to the anti human Fc/biotin resulting in a fluorescent identifying label on sUL18/Fc which is bound to cells. The cells were analyzed for any bound protein using

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fluorescent detection flow cytometry. The results indicated that UL18 binds well to B cell lines CB23, RAJI and MP-1; monocytic cell lines Thp-1 and U937; and primary B cell and primary monocytes. UL18 does not bind detectably to T cell lines nor does it bind to primary T cells.

Example 3

Isolating a P3G2 cDNA and Polypeptide

The following describes screening cDNA of one of the cell lines found to bind UL18 and the isolation of a novel polypeptide expressed by the cell line. A CB23 cDNA library in the mammalian expression vector pDC406, prepared as described in U.S. Pat. No. 5,350,683 (incorporated herein by reference) was obtained and plasmid DNA was isolated from pools consisting of approximately 2,000 clones per pool. The isolated DNA was transfected into CV1-EBNA cells (ATCC CRL 10478) using DEAE-dextran followed by chloroquine treatment. The CV1-EBNA cells were maintained in complete medium (Dulbecco's modified Eagles' media containing 10% (v/v) fetal calf serum, 50 U/mL penicillin, 50 U/mL streptomycin, and 2 mM L-glutamine) and were plated to a density of approximately 2×10^5 cells/well in single-well chambered slides. The slides had been pre-treated with 1 mL of a solution of 10 μ g/mL human fibronectin in PBS for 30 minutes followed by a single washing with PBS. Media was removed from adherent cells growing in a layer and replaced with 1.5 mL complete medium containing 66.6 μ M chloroquine sulfate. About 0.2 mL of a DNA solution (2 μ g DNA, 0.5 mg/mL DEAE-dextran in complete medium containing chloroquine) was added to the cells and the mixture was incubated at 37 C for about five hours. Following incubation, the media was removed and the cells were shocked by addition of complete medium containing 10% DMSO (dimethyl-sulfoxide) for 2.5 minutes. Shocking was followed by replacing the solution with fresh complete medium. The cells were grown in culture for two to three days to permit transient expression of the inserted DNA sequences. These conditions led to a 30% to 80% transfection frequency in surviving CV1-EBNA cells.

Each slide was incubated with 1 mL of UL18:Fc at a concentration of 1 μ g/mL in binding buffer (RPMI 1640 containing 25 mg/mL bovine serum albumin, 2 mg/mL sodium azide, 20 mM Hepes at pH 7.2, and 50 mg/mL nonfat dry milk) at room temperature for 1 hour. The incubated slides were washed with the binding buffer and then incubated with Fc specific 125 I-mouse anti-human IgG (see Goodwin et al., *Cell* 73:447-456, 1993). This was followed by a second wash with buffer after which the slides were fixed with a 2.5% glutaraldehyde/PBS solution, washed with PBS solution and allowed to air dry. The dried slides were dipped in Kodak GTNB-2 photographic emulsion (6 \times dilution in water). After air drying, the slides were placed in a dark box and refrigerated. After three days the slides were developed in Kodak D19 developer, rinsed in water and fixed in Agfa G433C fixer. The fixed slides were individually examined under a microscope at 25-40 \times magnification. Positive cells demonstrating binding of sUL18:Fc were visualized by the presence of autoradiographic silver grains against the film background. Two positive pools were identified. Bacterial clones from each pool were titered and plated to provide plates containing approximately 200 colonies each. Each plate was scraped to provide pooled plasmid DNA for transfection into CV1-EBNA cells and screening as described above. Following subsequent breakdowns and screenings, two positive individual colonies were obtained. The cDNA inserts of the two positive clones

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were 2922 and 2777 nucleotides in length as determined by automated DNA sequences. The coding regions of the two inserts, designated P3G2 and 18A3 were 1953 (nucleotides 310-2262) and 1959 (nucleotides 168-2126) nucleotides, respectively. The two cDNA clones encode proteins that are substantially similar and probably represent different alleles of the same gene.

The cDNA sequence and encoded amino acid of P3G2 are presented in SEQ ID NO:1 and SEQ ID NO:2, respectively. The cDNA sequence and encoded amino acid of 18A3 are presented in SEQ ID NO:3 and SEQ ID NO:4, respectively. The P3G2 amino acid sequence (SEQ ID NO:2) has a predicted signal peptide of 16 amino acids (amino acids 1-16); an extracellular domain of 442 amino acids (amino acids 17-458); a transmembrane domain of 25 amino acids (amino acids 459-483) and, a cytoplasmic domain of 167 amino acids (amino acids 484-650). The extracellular domain includes four immunoglobulin-like domains. Ig-like domain I includes approximately amino acids 17-118; Ig-like domain II includes approximately amino acids 119-220; Ig-like domain III includes approximately amino acids 221-318; and Ig-like domain IV includes approximately amino acids 319-419. Significantly, the cytoplasmic domain of this polypeptide includes four ITIM motifs, each having the consensus sequence of YxxL/V. The first ITIM motif pair is found at amino acids 533-536 and 562-565 and the second pair is found at amino acids 614-617 and 644-647. The amino acid sequence of 18A3 is nearly identical having the features describes above.

The features of these encoded polypeptides are consistent with a type I transmembrane glycoprotein.

Example 4

Preparing P3G2 Fusion Protein

The following describes procedures used to generate a P3G2 fusion protein which was then used to identify cell lines to which it binds and finally isolate a normal cell-surface P3G2 ligand which is distinct from UL18. A fusion protein of the extracellular region of P3G2 and the mutein human Fc region (sP3G2:Fc) was prepared by first isolating cDNA encoding the extracellular region of P3G2 using primers which flank the extracellular region of P3G2. The primers were synthesized with Sal I and Bgl II restriction sites inserted at the 5' and 3' termini so that the PCR amplified cDNA introduced Sal I and Bgl II restriction sites at the 5' and 3' ends, respectively. The primers had the following sequences:

(SEQ ID NO: 5)

Sal I
5' - TAT GTC GAC CAT GAC CCC CAT CCT CAC GGT - 3'

(SEQ ID NO: 6)

Bgl II Xa
5' - TAT GGG CTC TGC TCC AGG AGA AGA TCT TCC TTC
TAT AAC CCC CAG GTG CCT T

The conditions for the PCR reaction were as described above and the template was the full length gene P3G2 gene isolated as described in Example 3 above.

To prepare a vector construct for expressing fusion protein sP3G2:Fc for use in cell binding studies, the mutein human Fc region of IgG1 was cut from the plasmid described above in Example 1 using Bgl II and Not I restriction enzymes. The Bgl II site on the sP3G2 gene was used to ligate the sP3G2

gene DNA to the Bgl II site on the human mutein Fc gene to form a sP3G2/Fc fusion DNA construction having an N-terminal Sal I restriction site and a terminal Not I restriction site. This fusion sP3G2:Fc DNA construct was then ligated into pDC409 expression vector at its Sal I and Not I sites to form a 409/sP3G2/Fc DNA construct.

The monkey cell line COS-1 (ATCC CTL-1650) was used to confirm expression of the fusion protein. COS-1 cells in 6-well plates (2×10^5 cells per well) were transfected with about 2 μg of the DNA construct 409/sP3G2/Fc per well. The cells were cultured in 5% FBS/DMEM/F12 (available from GIBCO) and at day two or three following transfection, the cells were starved for 1 hour in cysteine/methionine depleted RPMI and the transfected cells were metabolically labeled with 100 $\mu\text{Ci}/\text{mL}$ of ^{35}S -Met/Cys for 4 hours. The supernatant was spun clear to removed loose cells and debris and 150 μL of the supernatant was incubated with 100 μL of RIPA buffer and 50 μL of 50% Protein A-Sepharose solid support beads at 4° C. for 1 hour. After washing the solid support with RIPA to remove unbound material, fusion protein bound to the Protein A-Sepharose solid support was eluted from the Protein A-Sepharose using 30 μL of SDS-PAGE reducing sample buffer and then heated at 100° C. for 5 minutes. The eluant was then electrophoresed on a 4-20% SDS polyacrylamide gradient gel with ^{14}C labeled protein molecular weight markers. After electrophoresis the gel was fixed with 8% acetic acid and enhanced at room temperature for 20 minutes with Amplifier available from Amersham. After drying the gel under vacuum it was exposed to x-ray film. Film analysis confirmed that the expected protein, having a molecular weight of 120-130 kDa, was expressed.

Once fusion protein expression was verified, large scale cultures of transfected cells were grown to accumulate supernatant from COS-1 cells expressing the fusion protein as described in Example 1 above. The P3G2/Fc fusion protein was purified according to the procedure described in Example 3 above using the BioCad system and the POROS 20A column from PerSeptive Biosystems. The pooled eluted protein was analyzed using SDS PAGE with silver staining, confirming expression.

Example 5

Generating LIR-P3G2 Antibody

The following example describes generating monoclonal antibody to P3G2 that was used in flow cytometry analysis to identify cells on which P3G2 is expressed. Purified P3G2/Fc fusion protein was prepared by COS-1 cell expression and affinity purification as described in Example 4. The purified protein or cells transfected with an expression vector encoding the full length protein can generate monoclonal antibodies against P3G2 using conventional techniques, for example those techniques described in U.S. Pat. No. 4,411,993. Briefly BALB-C mice were immunized at 0, 2 and 6 weeks with 10 μg P3G2/Fc. The primary immunization was prepared with TITERMAX adjuvant, from Vaxcell, Inc., and subsequent immunization were prepared with incomplete Freund's adjuvant (IFA). At 11 weeks, the mice were IV boosted with 3-4 μg P3G2 in PBS. Three days after the IV boost, splenocytes were harvested and fused with an Ag8.653 myeloma fusion partner using 50% aqueous PEG 1500 solution. Hybridoma supernatants were screened by ELISA using P3G2 transfected COS-1 cells in PBS at 2×10^3 cells per well and dried to polystyrene 96-well microtiter plates as the platecoat antigen. Positive supernatants were subsequently confirmed by FACS analysis and RIP using P3G2 transfected COS-1 cells. Hybri-

domas were cloned and followed using the same assays. Monoclonal cultures were expanded and supernatants purified by affinity chromatography using BioRad Protein A agarose.

The monoclonal antibodies to P3G2/Fc were used to screen cells and cell lines using standard flow cytometry procedures to identify cells on which P3G2 is expressed. Cell lines and cells screened in the flow cytometry analyses were CB23, CB39, RAJI, AK778, K299, PS-1, U937, THP-1, JURKAT and HSB2. For each cell line or cell sample screened, the procedure involved incubating approximately 100,000 of the cells blocked with 2% FCS (fetal calf serum), 5% normal Goat serum and 5% rabbit serum in PBS with 5 μg of FITC conjugated mouse anti-P3G2 antibody for 1 hour. Following the incubation the sample was washed 2 times with FACS buffer (2% FCS in PBS). The cells were analyzed for any bound protein using fluorescent detection flow cytometry to detect FITC. The results indicated that LIR-P3G2 antibody binds well to B cell lines CB23 and RAM; monocytic cell lines THP-1 and U937; and primary B cell and primary monocytes. The highest expression of LIR-P3G2 was shown on monocytes that stained brightly for CD16 and less brightly for CD14 and CD64. The antibody does not bind detectably to T cell lines nor does it bind detectably to primary T cells.

In a related experiment, the P3G2 antibody generated as described above was used in immunoprecipitation experiments. The immunoprecipitation analyses involved first surface biotinylating 2.5×10^6 monocytes by washing the cells with PBS and suspending the cells in a biotinylation buffer of 10 mM sodium borate and 150 mM NaCl at pH 8.8, followed by adding 5 μL of a 10 mg/mL solution of biotin-CNHS-ester (D-biotinoyl-e-aminocaproic acid-N-hydroxysuccinimide ester purchased from Amersham) in DMSO to the cells. After quenching the reaction with 10 μL of 1 M ammonium chloride per 1 mL of cells and washing the cells in PBS, the cells were lysed in 1 mL of 0.5% NP40-PBS and the lysate was recovered following centrifugation. Then 100 μL of 0.5% NP40-PBS was added to 150 μL of the lysate and the resulting mixture was incubated with 2 $\mu\text{g}/\text{mL}$ of antibody, at 4° C. for 16 hours. Fifty microliters of 50% Protein A-Sepharose slurry was added to the antibody mixture and the slurry was shaken at 4° C. for 1 hour. The slurry was centrifuged and the resulting pellet was washed with 0.75 mL of 0.5% NP40 in PBS six times. Protein bound to the Protein A-Sepharose was eluted with 30 μL of SDS-PAGE reducing sample buffer and heating at 100° C. for five minutes.

The eluted proteins were analyzed using 4-20% gradient SDS-PAGE with enhanced chemiluminescence (ECL) protein markers. Then the electrophoreses samples were transferred in a Western Blot onto nitrocellulose membranes. The membranes were treated with blocking reagent (0.1% Tween-20 and 3% nonfat dry milk in PBS) for one hour at room temperature and then they were washed once for 15 minutes followed and twice for 5 minutes with 0.1% Tween-20 in PBS. The washed membranes were incubated with 10 mL of 1:100 HRP-Streptavidin for 30 minutes and then washed 1 times for 15 minutes followed by 4 times for 5 minutes with 0.1% Tween-20 in PBS.

Bound streptavidin HRP was detected with ECL Detection Reagents purchased from Amersham and used according to manufacturer's instructions. The developed membranes were exposed to x-ray film and then visualized. The results showed

that LIR-P3G2 was immunoprecipitated from CB23 cells and P3G2 transfected COS-1 cells, indicating that P3G2 is expressed by these cells.

Example 6

Screening Cells and Cell Lines for Binding to P3G2

The following describes flow cytometry analyses used to identify cells and cell lines which bind to P3G2. The cells and cell lines tested were CB23, HSB2, MP-1, Jurkat, primary T cells, primary B cells, and primary NK cells. For each cell line or cell line tested the procedure involved washing the cells three times with FACS buffer (2% FCS in PBS with 0.2% azide) and incubating each sample (10^5 cells) in 100 μ L blocking buffer (2% FCS, 5% NGS, 5% rabbit serum in PBS) for one hour. For each cell line 4 test samples were prepared, one each having 0, 2, 5, or 10 μ g of W6/32 (ATCC HB-95) in 100 μ L blocking buffer added to the samples, respectively. W6/32 is an antibody against MHC Class I heavy chains (an anti HLA-A, B, and C molecule). Following the addition of the W6/32 solution, the samples were incubated on ice for 1 hour and then washed three times with 200 μ L of FACS buffer. Then 5 μ g of P3G2/Fc in blocking buffer was added to each sample and they were incubated on ice for one hour. The P3G2/Fc competes with W6/32 for binding sites on the cells.

Following the incubation, the cells were washed three times with 200 μ L of FACS buffer and treated with mouse anti human Fc/biotin and SAPE for 45 minutes. This treatment causes the anti human Fc/biotin to bind to any cell bound sP3G2/Fc and the SAPE to bind to the anti human F/Biotin. Since the SAPE is a fluorescing compound its detection using appropriate excitation and emission conditions positively identifies cell bound P3G2/Fc. Finally the treated cells were washed three times with FACS buffer and subjected to flow cytometry to identify cells bound to protein.

The results demonstrated that W6/32 competed with P3G2 for binding to all cells and cell lines tested. The P3G2 binding was totally blocked at 5 μ g W6/32 indicating that W6/32 and P3G2 are binding to the same or overlapping sites on the MHC Class I heavy chains.

Example 7

Screening HSB2 cDNA Library to Isolate a P3G2 Binding Ligand

The following describes screening a cDNA library from of one of the cell lines, HSB-2, a T lymphoblastic leukemia cell line, found to bind P3G2, and identifying a P3G2 binding ligand. An HSB2 cDNA library in the mammalian expression vector pDC302, was prepared as generally described in U.S. Pat. No. 5,516,658 and specifically in Kozlosky et al. *Oncogene* 10:299-306, 1995. Briefly, mRNA was isolated from sorted HSB-2 cells and a first cDNA strand was synthesized using 5 μ g polyA⁺ and the reverse transcriptase AMV RTase from Life Science. The second cDNA strand was synthesized using DNA polymerase I from BRL at concentration of 1.5 U/ μ L. Using standard techniques as described in Haymerle et al., *Nucl. Acids Res.* 14:8615, 1986, the cDNA was ligated into the appropriate site of the pDC302 vector.

E. coli. strain DH5 α cells were transformed with the cDNA library in pDC302. After amplifying the library a titer check indicated that there was a total of 157,200 clones. The transformed cells were plated into 15 different plates. Plasmid DNA was isolated from pools consisting of approximately 2,000 clones per pool. The isolated DNA was transfected into

CV1-EBNA cells (ATCC CRL 10478) using DEAE-dextran followed by chloroquine treatment. The CV1-EBNA cells were maintained in complete medium (Dulbecco's modified Eagles' media containing 10% (v/v) fetal calf serum, 50 U/mL penicillin, 50 U/mL streptomycin, and 2 mM L-glutamine) and were plated to a density of approximately 2×10^5 cells/well in single-well chambered slides. The slides had been pre-treated with 1 mL of a solution of 10 μ g/mL human fibronectin in PBS for 30 minutes followed by a single washing with PBS. Media was removed from adherent cells growing in a layer and replaced with 1.5 mL complete medium containing 66.6 μ M chloroquine sulfate. About 0.2 mL of a DNA solution (2 μ g DNA, 0.5 mg/mL DEAE-dextran in complete medium containing chloroquine) was added to the cells and mixture was incubated at 37 C for about five hours. Following incubation media was removed and the cells were shocked by adding complete medium containing 10% DMSO for 2.5 minutes. After shocking the cells the complete medium was replaced with fresh complete medium and the cells were grown in culture for three days to permit transient expression of the inserted DNA sequences. These conditions led to a 30% to 80% transfection frequency in surviving CV1-EBNA cells.

Each slide was incubated with 1 mL of P3G2:Fc at a concentration of 0.45 μ g/mL in binding buffer (RPMI 1640 containing 25 mg/mL bovine serum albumin, 2 mg/mL sodium azide, 20 mM Hepes at pH 7.2, and 50 mg/mL nonfat dry milk) at room temperature for 1 hour. After incubating the slides, they were washed with binding buffer and then incubated with Fc specific ¹²⁵I-mouse anti-human IgG (see Goodwin et al. *Cell* 73:447-456, 1993). This was followed by a second wash with buffer after which the slides were fixed with a 2.5% glutaraldehyde/PBS solution, washed in PBS and allowed to air dry. The slides were dipped in Kodak GTNB-2 photographic emulsion (6 \times dilution in water). After air drying the slides were placed in a dark box and refrigerated. After three days the slides were developed in Kodak D19 developer, rinsed in water and fixed in Agfa G433C fixer. The fixed slides were individually examined under a microscope at 25-40 \times magnification. Positive pools demonstrating binding of sP3G2:Fc were visualized by the presence of autoradiographic silver grains against the film background. Two positive pools were titered and plated to provide plates containing approximately 200 colonies each. Each plate was scraped to provide pooled plasmid DNA for transfection into CV1-EBNA cells and screening as described above. Following subsequent breakdowns and screenings, one positive individual colony was obtained for each pool. The cDNA insert of the positive clones were identified as HLA-B44 and HLA-A2, class I MHC antigens.

Example 8

Northern Blot Analysis

Since the experiments described in Example 4 resulted in the detection of LIR-P3G2 surface expression on a number of cell lines, conventional Northern Blot analysis procedures were used to study the expression of LIR-P3G2 and any LIR-P3G2 related mRNAs in different tissue types. The cell lines selected for Northern Blot analysis were RAJI, PBT, PBM, YT, HEP3B, HELA, KB, KG-1, IMTLH, HPT, HFF, THP-1, and U937. The following describes the Northern Blot analysis and the analysis results.

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The cDNA encoding the extracellular region of P3G2 was isolated using primers which flank the extracellular region of P3G2 and having the following sequences:

(SEQ ID NO: 5)

Sal I

5' - TAT GTC GAC CAT GAC CCC CAT CCT CAC GGT - 3'

(SEQ ID NO: 27)

Bgl II

5' - TAT AGA TCT ACC CCC AGG TGC CTT CCC AGA CCA

The PCR template was the full length P3G2 gene isolated as described in Example 3 above. The conditions for the PCR reaction were as follows: One cycle at 95° C. for 5 minutes; 30 cycles which included 95° C. for 45 seconds, 64° C. for 45 seconds and 72° C. for 45 seconds; and, one cycle at 72° C. for 5 minutes. The PCR product was cloned into PCR II vector, purchased from Invitrogen, in accordance with the supplier's instructions. The isolated DNA encoding the extracellular region of P3G2 was used to make a riboprobe with the Ambion MAXISCRIPt Kit according to the manufacturer's instructions.

Northern blots containing poly A+ selected RNA or total RNA from a variety of human cell lines were prepared by resolving RNA samples on a 1.1% agarose-formaldehyde gel, blotting onto Hybond-N as recommended by the manufacturer (Amersham Corporation) and staining with methylene blue to monitor RNA concentrations. The blots were prepared using 1 µg of the PolyA+ RNA or 10 µg of total RNA and each blot was probed with 10⁶ cpm/mL RNA extracellular P3G2 riboprobe, prepared as just described, at 63° C. for 16 hours. The probed blots were washed with 2×SSC at 63° C. for 30 minutes 2 times; 1×SSC at 63° C. for 30 minutes 2 times; and, 0.1×SSC at 63° C. for 5 minutes 2 times.

The probed blots were autoradiographically developed. The developed blots showed that the P3G2 RNA hybridized to a 3.5 kb RNA expressed by RAJI, CB23 and U937; an approximately 1.5 kb RNA expressed by THP-1; and multiple RNAs ranging from 1.5 kb to 3.5 kb expressed by PBM. These results suggest that different genes having extracellular domains similar in structure to that of P3G2 may be expressed by peripheral blood monocytes.

Example 9

Probing PBM cDNA Library to Isolate LIR Polypeptides

The following describes steps taken to screen a peripheral blood monocyte cDNA library to isolate polypeptides relating to the P3G2 polypeptide using conventional Southern Blot methodologies. A peripheral blood monocyte cDNA library was prepared using substantially the same procedures described in Example 7.

DNA from an initial 15 pools of cDNA having 10,000 clones per pool was digested with Bgl II restriction enzyme and electrophoresed on a 1% agarose gel at 100 V for 2 hours. Southern Blots were prepared by electroblotting the electrophoresed DNA in 0.55% TBE buffer onto Hybond membranes. The blotted DNA was denatured in 0.5 M NaOH in 0.6M NaCl solution for 5 minutes and then neutralized in 0.5 M TRIS in 1.5 M NaCl at pH 7.8 for 5 minutes. The membranes were placed in a STRATALINKER UV crosslinker for 20 seconds to crosslink the blotted DNA to the membrane. The membrane and bound DNA were placed in pre-hybridization solution of 10×Denhart's Solution, 0.05M TRIS at pH

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7.5, 0.9M NaCl, 0.1% sodium pyrophosphate, 1% SDS and 200 µg/mL salmon sperm DNA at 63° C. for 2 hours and then the bound DNA was probed with ³²P labeled probe of DNA encoding the extracellular region of LIR-P3G2, including the signal peptide and Sal I and Bgl II restriction sites. The concentration of the DNA probe in hybridization solution was 10⁶ CPM per mL of hybridization solution. The probed blots were incubated for 16 hours at 63° C. and then washed with 2×SSC at 63° C. for 1 hour with one solution change; 1× with SSC at 63° C. for one hour with one solution change; and, with 0.1×SSC at 68° C. for 45 minutes with one solution change. After drying the blots they were autoradiographically developed and visualized for DNA bands which hybridized to the P3G2 extracellular DNA probe.

The results of the autoradiography visualization indicated that all pools contained DNA which hybridized to the probe. One pool showing 7 positive DNA bands was selected and subsequently subdivided to 10 pools having 3,000 clones per pool. Applying subsequent Southern Blotting methodologies to the 10 pools resulted in one pool showing 9 positively hybridizing DNA sequences. Single hybridizing clones were isolated by standard colony hybridization techniques.

Duplicate bacterial colonies on filters were probed with the P3G2 extracellular probe described above at a concentration of 500,000 cpm/mL at 63° C. for 16 hours. The hybridized filters were washed with 2×SSC at 63° C. for 30 minutes; with 1×SSC at 63° C. for 30 minutes; and finally with 0.1×SSC at 68° C. for 15 minutes.

Forty-eight clones were visualized as hybridizing on duplicate filters by autoradiography and DNA obtained from these clones using standard DNA preparation methodologies was digested with Bgl II. Then Southern Blots of the digests were obtained and probed with the P3G2 extracellular probe described above. Seven different sized cloned inserts were identified as positively hybridizing to the P3G2 probe. The nucleotide sequence of each of the inserts was obtained using automated sequencing technology. Of the 8 different cloned inserts, one was identical in sequence to LIR-P3G2. The others were identified as DNA encoding polypeptides of the new LIR family of polypeptides. The nucleotide sequences (cDNA) of the isolated LIR family members are presented in SEQ ID NO:7 (designated pbm25), SEQ ID NO:9 (designated pbm8), SEQ ID NO:11 (designated pbm36-2), SEQ ID NO:13 (designated pbm36-4); SEQ ID NO:15 (designated pbmhh); SEQ ID NO:17 (designated pbm2) and SEQ ID NO:19 (designated pbm17). The amino acid sequences encoded thereby are presented in SEQ ID NO:8 (designated pbm25), SEQ ID NO:10 (designated pbm8), SEQ ID NO:12 (designated pbm36-2), SEQ ID NO:14 (designated pbm36-4), SEQ ID NO:16 (designated pbmhh); SEQ ID NO:18 (designated pbm2); and SEQ ID NO:20 (designated pbm17).

Example 10

Screening a Human Dendritic Cell cDNA Library for LIR cDNA Sequences

The following describes the isolation and identification of an LIR family member by screening a human bone marrow-derived dendritic cell cDNA library in the λ Zap vector with a radiolabeled Hh0779 cDNA fragment. The Hh0779 cDNA fragment is a 0.7 kb insert of the Hh0779 clone previously isolated from a human dendritic cell cDNA library and obtained by restriction digestion with the enzymes PstI and SpeI. The Hh0779 cDNA fragment was labeled with [α-³²P] dCTP using the DECAprime II DNA labeling kit purchased from Ambion.

The λ Zap cDNA library was plated at a density of 20,000 pfu per plate to provide a total of 480,000 plaques for the initial screening. The λ Zap cDNA was blotted in duplicate onto Hybond membranes, purchased from Amersham, and then denatured in a solution of 0.5N NaOH and 0.5M NaCl for 5 minutes. The membranes were neutralized in a solution of 0.5M Tris (pH 7.8) and 1.5M NaCl for 5 minutes, and then washed in 2 \times SSC for 3 minutes. The cDNA was crosslinked to the Hybond membranes using a STRATALINKER UV crosslinker in the auto setting.

The membranes were pre-hybridized at 65° C. for 2.25 hours in hybridization buffer containing 10 \times Denhardt's, 0.05M Tris (pH 7.5), 0.9M NaCl, 0.1% sodium pyrophosphate, 1% SDS and 4 mg/mL heat denatured salmon sperm DNA. After the pre-hybridization, the radiolabeled Hh0779 cDNA was added to the hybridization buffer to a final concentration of 0.54 \times 10⁶ cpm/mL. After 24 hours of hybridization, the membranes were washed in 0.25 \times SSC, 0.25% SDS at 65° C. for 1.5 hours. The blots were then exposed to autoradiographic film to visual positive clones.

A total of 146 positive clones showing hybridization signals in both membranes of a duplicate set were identified, isolated, and saved for future use. Of the 146 clones, 35 were selected for secondary screening. The selected clones were plated at low density and single clones were isolated after hybridization to the HH0779 probe using the hybridization conditions described above. The plasmids were then isolated from the λ Zap clones using the VCSM13 helper phage purchased from Stratagene. The plasmid DNA was analyzed by restriction digestion and PCR, and the clones containing the 24 largest inserts were selected and sequenced. Of the 24 sequenced clones, 6 encoded LIR-P3G2, 3 encoded LIR-pbm2, 8 encoded LIR-pbm36-4 and LIR-pbm36-2, 1 encoded LIR-pbm8, 2 encoded LIR-pmbhh, and 1 encoded a novel sequence designated LIR-pbmnew. Three clones were identified as encoding amino acid sequences that are not relevant to the LIR polypeptide family.

Example 11

Association of LIR-P3G2 and LIR-pbm8 with Tyrosine Phosphatase, SHP-1

The following describes the tests performed to demonstrate that LIR-P3G2 and LIR-pbm8 associate with SHP-1. Human monocytes were cultured in RPMI medium supplemented with 10% FBS, concentrated by centrifugation and finally subdivided into two aliquots. One aliquot was stimulated with a solution of 50 mM/mL sodium pervanadate for 5 minutes. The second aliquot was not stimulated. After stimulation, the cells in each aliquot were immediately lysed in RIPA buffer containing 1% NP-40, 0.5% sodium deoxycholate, 50 mM Tris pH8, 2 mM EDTA, 0.5 mM sodium orthovanadate, 5 mM sodium fluoride, 25 mM β -glycerol phosphate, and protease inhibitors. Samples of 24 \times 10⁶ cell equivalents were incubated for 2 hours at 4° C. with either 5 μ g/mL of anti-SHP-1 antibody purchased from Transduction Laboratories, or 5 μ g/mL of an isotype-matched antibody control (anti-Flag-MS IgG1). The resulting immunocomplexes were precipitated by incubation with protein G-agarose (Boehringer Mannheim), washed, and resuspended in 40 mL of 2 \times SDS-PAGE sample buffer. Twenty microliters of each immunoprecipitate were loaded onto electrophoresis gels, electrophoresed under reducing conditions, and transferred to nitrocellulose membranes purchased from Amersham. Western blots were probed with anti-LIR-P3G2 monoclonal antibody sera and anti-LIR-pbm8 monoclonal

antibody antisera and the immunocomplexes were detected by enhanced chemiluminescence (NEN).

A protein having a molecular weight of approximately 120 kDa, corresponding to LIR-P3G2 was readily detected in SHP-1 immunoprecipitates, but not the immunoprecipitates generated with the anti-Flag-MS antibody control. Similarly, a protein of 90-100 kDa, corresponding to LIR-pbm8, was detected in SHP-1 immunoprecipitates, but not in the control immunoprecipitates. Neither the LIR-P3G2 band nor the LIR-pbm8 band was seen in the absence of sodium pervanadate treatment. This confirms that tyrosine phosphorylation of LIR-P3G2 is essential for the association of LIR-P3G2 and SHP-1 and phosphorylation of LIR-pbm8 is essential for the association of LIR-pbm8 and SHP-1.

To study the inhibition of Fc γ RI-mediated tyrosine phosphorylation events upon LIR coligation, peripheral blood monocytes were incubated with or without 10 μ g/mL of F(ab)₂ version of a number of antibodies (α -LIR-1+ α -LIR-2, α -CD11c, α CD14, α CD64, α -CD64+ α -LIR-1, α -CD64+ α -LIR-2, α -CD64+ α -LIR-1+ α -LIR-2, α CD64+ α -CD11c, α -CD64+ α -CD14). This was followed with crosslinking with 30 μ g/mL of polyclonal F(ab)₂ goat anti-mouse. Cell lysates were immunoprecipitated overnight with anti-phosphotyrosine conjugated agarose, electrophoresed, and transferred onto nitrocellulose. Western blotting was performed using a combination of PY-20 and 4G10 HRP-conjugated anti-phosphotyrosine mAbs. This data demonstrates the specific inhibition of Fc γ RI-mediated tyrosine phosphorylation events upon LIR-P3G2 and LIR-pbm8 coligation.

Example 12

Generating Antibodies Immunoreactive with LIR Polypeptides

The following describes generating monoclonal antibody immunoreactive with LIR family members. A purified LIR polypeptide is prepared by COS-1 cell expression and affinity purification as described in Example 4. The purified protein or cells transfected with an expression vector encoding the full length protein can generate monoclonal antibodies against the LIR polypeptide using conventional techniques, for example those techniques described in U.S. Pat. No. 4,411,993. Briefly BALB-C mice are immunized at 0, 2 and 6 weeks with 10 μ g of the LIR polypeptide. The primary immunization is prepared with TITERMAX adjuvant and subsequent immunizations are prepared with incomplete Freund's adjuvant (IFA). At 11 weeks, the mice are IV boosted with 3-4 μ g the LIR polypeptide in PBS. Three days after the IV boost, splenocytes are harvested and fused with an Ag8.653 myeloma fusion partner using 50% aqueous PEG 1500 solution. Hybridoma supernatants are screened by ELISA using the LIR transfected cells in PBS at 7 \times 10³ cells per well and dried to polystyrene 96-well microtiter plates as the platecoat antigen. Positive supernatants are subsequently confirmed by FACS analysis and RIP using LIR transfected cells. Hybridomas are cloned and followed in the same manner of screening. Monoclonal cultures are expanded and supernatants purified by affinity chromatography.

Example 13

Flow Cytometric Analysis For Expression of LIR-P3G2 and LIR-pbm8 on Lymphoid and Myeloid Cells

In order to compare the differential expression and distribution of LIR-P3G2 and LIR-pbm8 on lymphocyte popula-

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tions, freshly isolated peripheral blood mononuclear cells (PBMC) were stained with PE-labeled anti-CD3, anti-CD19, or anti-CD56 mAb in the presence of either biotin labeled anti-LIR-P3G2 or anti LIR-pbm8 mAb. Then the stained cells were treated with APC-labeled streptavidin. Density plots representing 5×10^4 events were collected on a FACScaliber (from Beckton Dickinson). The results demonstrated that LIR-P3G2 is expressed on 80%-95% of CD19⁺B cells, on 5%-15% CD3⁺T cells, and on 10%-30% CD56⁺NK cells. On the cells examiner from the same 12 donors, LIR-pbm8 expression was not detected on CD19⁺B cells, CD3⁺T cells, and CD56⁺NK cells.

Countercurrent elutriated fractions containing a high percentage of circulating monocytes and dendritic cells (DC) were obtained. The monocytes were characterized according to the phenotypes subsets CD14⁺CD16⁻ and CD14⁺CD16⁺. The peripheral blood DC were characterized with the phenotype CD33⁺CD14⁺CD16⁻HLA-DR⁺. The monocytes subsets and DC's were stained with FITC-labeled antiCD14, PE-labeled anti CD3, perCp-labeled antiHLA-DR, and either biotin-labeled anti-CD16, anti-LIR-P3G2, or anti LIR-pbm8. Then the stained cells were treated with APC-labeled streptavidin. Both monocyte subsets co-express similar levels of LIR-P3G2 and LIR-pbm8, with the highest LIR-P3G2 and LIR-pbm8 expression detected on the CD14⁺CD16⁺ subset. Blood DC express lower levels of LIR-P3G2 and LIR-pbm8 compared to monocytes. The results of these experiments demonstrate the LIR-P3G2 is expressed on lymphocytes, monocytes and DC, and LIR-pbm8 is expressed on monocytes and DC.

Example 14

Screening LIR-P3G2 and LIR-pbm8 Binding to HLA Class I Alleles

The following describes flow cytometry analyses used to screen LIR-P3G2 and LIR-pbm8 for binding to HLA Class I alleles. The B lymphoblastoid class I-deficient 721.221 cell line, untransfected or transfected with a panel of HLA class I alleles was used for staining. LIR-P3G2/Fc and LIR-pbm8/Fc fusion proteins were used in the binding studies and both bound detectably to seven of the eleven HLA-A, HLA-B and HLA-C alleles that were tested. In general, LIR-P3G2/Fc and LIR-pbm8/Fc bind with higher affinity to HLA-B alleles than to HLA-A or HLA-C alleles. W6/32 (ATCC HB-95), an antibody against MHC Class I heavy chains (an anti HLA-A, B, and C molecule) inhibits LIR-P3G2/Fc and LIR-pbm8/Fc binding to all class I transfectants. Finally, LIR-P3G2 and LIR-pbm8 binding does not correlate with the MHC class I

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expression levels. Thus, LIR-P3G2 and LIR-pbm8 bind to several HLA-A, -B, and -C alleles, and recognize a similar broad spectrum of MHC class I specificities.

Example 15

Isolation of LIR-9 m1, LIR-9m, LIR-9s1, LIR-9s2 and LIR-10

In the course of high throughput sequencing of a human dendritic cell cDNA library, it was noted that the sequence of an incomplete cDNA (clone ss4894) was strikingly similar to the nucleotide sequences of LIRs 6a, 6b and 7, thus suggesting that ss4894 was a member of the LIR gene family. To obtain the remainder of this cDNA clone, the Rapid Amplification cDNA Extension system (RACE) was used to amplify a human leukocyte cDNA library (Chenchik et al., *A Laboratory Guide to RNA: Isolation, Analysis, and Synthesis*, Ed. Kreig, P. A. (Wiley-Liss, Inc.), pages 273-321). The first round of amplification employed one primer corresponding to the RACE adapter at the 5' end of the cDNAs, and a second primer corresponding to sequences near the 3' end of ss4894. This effort yielded several clones that contained sequence that was highly homologous though not identical to that of ss4894 and that extended upstream beyond an initiating methionine codon. These clones, however, lacked some of the sequence at the 3' end of the coding region. In an effort to obtain an entire coding region, another round of RACE sequencing was performed, this time using a first primer from near the 5' end of the first RACE products, and a second primer corresponding to the 3' adapter. This effort yielded five clones containing LIR inserts, four of which are closely related and appear to encode variants of the same gene. These four closely related cDNA sequences were designated LIR-9 m1, LIR-9 m2, LIR-9s1 and LIR-9s2 (SEQ ID NOS:29, 31, 33 and 35). The fifth of the clones obtained using this last set of primers represented a different gene, which has been designated LIR-10 (SEQ ID NO:37).

All four of the LIR-9 clones encode variants of the same protein, and are presumed to be the products of alternative splicing. The proteins encoded by LIR-9m1 (SEQ ID NO:30) and LIR-9s1 (SEQ ID NO:34) contain a 12 amino acid insert that is absent from LIR-9 m2 (SEQ ID NO:32) and LIR-9s2 (SEQ ID NO:36). The soluble forms of the LIR-9 protein, i.e., LIR-9s1 and LIR-9s2, diverge near their carboxy termini from the membrane forms, i.e., LIRs-9 m1 and -9 m2. This divergence presumably is due to different exons being used by the soluble and membrane forms to encode that region of the protein.

SEQUENCE LISTING

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60

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gctggagggga cgactgccat gcaccgaggg ctcacccatc cacagagcag ggcagtggga	300
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Leu Trp Ala Glu Pro Gly Ser Val Ile Thr Gln Gly Ser Pro Val Thr	
35 40 45	
ctc agg tgt cag ggg ggc cag gag acc cag gag tac cgt cta tat aga	495
Leu Arg Cys Gln Gly Gly Gln Glu Thr Gln Glu Tyr Arg Leu Tyr Arg	
50 55 60	
gaa aag aaa aca gca ccc tgg att aca cgg atc cca cag gag ctt gtg	543
Glu Lys Lys Thr Ala Pro Trp Ile Thr Arg Ile Pro Gln Glu Leu Val	
65 70 75	
aag aag ggc cag ttc ccc atc cca tcc atc acc tgg gaa cat gca ggg	591
Lys Lys Gly Gln Phe Pro Ile Pro Ser Ile Thr Trp Glu His Ala Gly	
80 85 90	
cgg tat cgc tgt tac tat ggt agc gac act gca ggc cgc tca gag agc	639
Arg Tyr Arg Cys Tyr Tyr Gly Ser Asp Thr Ala Gly Arg Ser Glu Ser	
95 100 105 110	
agt gac ccc ctg gag ctg gtg gtg aca gga gcc tac atc aaa ccc acc	687
Ser Asp Pro Leu Glu Leu Val Val Thr Gly Ala Tyr Ile Lys Pro Thr	
115 120 125	
ctc tca gcc cag ccc agc ccc gtg gtg aac tca gga ggg aat gta acc	735
Leu Ser Ala Gln Pro Ser Pro Val Val Asn Ser Gly Gly Asn Val Thr	
130 135 140	
ctc cag tgt gac tca cag gtg gca ttt gat ggc ttc att ctg tgt aag	783
Leu Gln Cys Asp Ser Gln Val Ala Phe Asp Gly Phe Ile Leu Cys Lys	
145 150 155	
gaa gga gaa gat gaa cac cca caa tgc ctg aac tcc cag ccc cat gcc	831
Glu Gly Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His Ala	
160 165 170	
cgt ggg tgc tcc cgc gcc atc ttc tcc gtg ggc ccc gtg agc ccg agt	879
Arg Gly Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Ser	
175 180 185 190	
cgc agg tgg tgg tac agg tgc tat gct tat gac tgc aac tct ccc tat	927
Arg Arg Trp Trp Tyr Arg Cys Tyr Ala Tyr Asp Ser Asn Ser Pro Tyr	
195 200 205	
gag tgg tct cta ccc agt gat ctc ctg gag ctc ctg gtc cta ggt gtt	975
Glu Trp Ser Leu Pro Ser Asp Leu Leu Glu Leu Leu Val Leu Gly Val	
210 215 220	
tct aag aag cca tca ctc tca gtg cag cca ggt cct atc gtg gcc cct	1023
Ser Lys Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Ile Val Ala Pro	
225 230 235	
gag gag acc ctg act ctg cag tgt ggc tct gat gct ggc tac aac aga	1071
Glu Glu Thr Leu Thr Leu Gln Cys Gly Ser Asp Ala Gly Tyr Asn Arg	
240 245 250	
ttt gtt ctg tat aag gac ggg gaa cgt gac ttc ctt cag ctc gct ggc	1119
Phe Val Leu Tyr Lys Asp Gly Glu Arg Asp Phe Leu Gln Leu Ala Gly	
255 260 265 270	
gca cag ccc cag gct ggg ctc tcc cag gcc aac ttc acc ctg ggc cct	1167
Ala Gln Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro	

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275					280					285						
gtg	agc	cgc	tcc	tac	ggg	ggc	cag	tac	aga	tgc	tac	ggt	gca	cac	aac	1215
Val	Ser	Arg	Ser	Tyr	Gly	Gly	Gln	Tyr	Arg	Cys	Tyr	Gly	Ala	His	Asn	
			290					295					300			
ctc	tcc	tcc	gag	tgg	tcg	gcc	ccc	agc	gac	ccc	ctg	gac	atc	ctg	atc	1263
Leu	Ser	Ser	Glu	Trp	Ser	Ala	Pro	Ser	Asp	Pro	Leu	Asp	Ile	Leu	Ile	
			305				310						315			
gca	gga	cag	ttc	tat	gac	aga	gtc	tcc	ctc	tcg	gtg	cag	ccg	ggc	ccc	1311
Ala	Gly	Gln	Phe	Tyr	Asp	Arg	Val	Ser	Leu	Ser	Val	Gln	Pro	Gly	Pro	
			320				325					330				
acg	gtg	gcc	tca	gga	gag	aac	gtg	acc	ctg	ctg	tgt	cag	tca	cag	gga	1359
Thr	Val	Ala	Ser	Gly	Glu	Asn	Val	Thr	Leu	Leu	Cys	Gln	Ser	Gln	Gly	
			335				340				345				350	
tgg	atg	caa	act	ttc	ctt	ctg	acc	aag	gag	ggg	gca	gct	gat	gac	cca	1407
Trp	Met	Gln	Thr	Phe	Leu	Leu	Thr	Lys	Glu	Gly	Ala	Ala	Asp	Asp	Pro	
			355					360							365	
tgg	cgt	cta	aga	tca	acg	tac	caa	tct	caa	aaa	tac	cag	gct	gaa	ttc	1455
Trp	Arg	Leu	Arg	Ser	Thr	Tyr	Gln	Ser	Gln	Lys	Tyr	Gln	Ala	Glu	Phe	
			370					375						380		
ccc	atg	ggt	cct	gtg	acc	tca	gcc	cat	gcg	ggg	acc	tac	agg	tgc	tac	1503
Pro	Met	Gly	Pro	Val	Thr	Ser	Ala	His	Ala	Gly	Thr	Tyr	Arg	Cys	Tyr	
			385					390					395			
ggc	tca	cag	agc	tcc	aaa	ccc	tac	ctg	ctg	act	cac	ccc	agt	gac	ccc	1551
Gly	Ser	Gln	Ser	Ser	Lys	Pro	Tyr	Leu	Leu	Thr	His	Pro	Ser	Asp	Pro	
			400				405					410				
ctg	gag	ctc	gtg	gtc	tca	gga	ccg	tct	ggg	ggc	ccc	agc	tcc	ccg	aca	1599
Leu	Glu	Leu	Val	Val	Ser	Gly	Pro	Ser	Gly	Gly	Pro	Ser	Ser	Pro	Thr	
			415				420				425				430	
aca	ggc	ccc	acc	tcc	aca	tct	ggc	cct	gag	gac	cag	ccc	ctc	acc	ccc	1647
Thr	Gly	Pro	Thr	Ser	Thr	Ser	Gly	Pro	Glu	Asp	Gln	Pro	Leu	Thr	Pro	
			435					440						445		
acc	ggg	tcg	gat	ccc	cag	agt	ggt	ctg	gga	agg	cac	ctg	ggg	ggt	gtg	1695
Thr	Gly	Ser	Asp	Pro	Gln	Ser	Gly	Leu	Gly	Arg	His	Leu	Gly	Val	Val	
			450					455						460		
atc	ggc	atc	ttg	gtg	gcc	gtc	atc	cta	ctg	ctc	ctc	ctc	ctc	ctc	ctc	1743
Ile	Gly	Ile	Leu	Val	Ala	Val	Ile	Leu								
			465				470						475			
ctc	ttc	ctc	atc	ctc	cga	cat	cga	cgt	cag	ggc	aaa	cac	tgg	aca	tcg	1791
Leu	Phe	Leu	Ile	Leu	Arg	His	Arg	Arg	Gln	Gly	Lys	His	Trp	Thr	Ser	
			480				485					490				
acc	cag	aga	aag	gct	gat	ttc	caa	cat	cct	gca	ggg	gct	gtg	ggg	cca	1839
Thr	Gln	Arg	Lys	Ala	Asp	Phe	Gln	His	Pro	Ala	Gly	Ala	Val	Gly	Pro	
			495				500				505				510	
gag	ccc	aca	gac	aga	ggc	ctg	cag	tgg	agg	tcc	agc	cca	gct	gcc	gat	1887
Glu	Pro	Thr	Asp	Arg	Gly	Leu	Gln	Trp	Arg	Ser	Ser	Pro	Ala	Ala	Asp	
			515					520						525		
gcc	cag	gaa	gaa	aac	ctc	tat	gct	gcc	gtg	aag	cac	aca	cag	cct	gag	1935
Ala	Gln	Glu	Glu	Asn	Leu	Tyr	Ala	Ala	Val	Lys	His	Thr	Gln	Pro	Glu	
			530					535						540		
gat	ggg	gtg	gag	atg	gac	act	cgg	agc	cca	cac	gat	gaa	gac	ccc	cag	1983
Asp	Gly	Val	Glu	Met	Asp	Thr	Arg	Ser	Pro	His	Asp	Glu	Asp	Pro	Gln	
			545				550						555			
gca	gtg	acg	tat	gcc	gag	gtg	aaa	cac	tcc	aga	cct	agg	aga	gaa	atg	2031
Ala	Val	Thr	Tyr	Ala	Glu	Val	Lys	His	Ser	Arg	Pro	Arg	Arg	Glu	Met	
			560				565					570				
gcc	tct	cct	cct	tcc	cca	ctg	tct	ggg	gaa	ttc	ctg	gac	aca	aag	gac	2079
Ala	Ser	Pro	Pro	Ser	Pro	Leu	Ser	Gly	Glu	Phe	Leu	Asp	Thr	Lys	Asp	
			575				580				585				590	
aga	cag	gcg	gaa	gag	gac	agg	cag	atg	gac	act	gag	gct	gct	gca	tct	2127

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Arg	Gln	Ala	Glu	Glu	Asp	Arg	Gln	Met	Asp	Thr	Glu	Ala	Ala	Ala	Ser		
			595						600						605		
gaa gcc ccc cag gat gtg acc tac gcc cag ctg cac agc ttg acc ctt 2175																	
Glu	Ala	Pro	Gln	Asp	Val	Thr	Tyr	Ala	Gln	Leu	His	Ser	Leu	Thr	Leu		
			610					615					620				
aga cgg aag gca act gag cct cct cca tcc cag gaa ggg ccc tct cca 2223																	
Arg	Arg	Lys	Ala	Thr	Glu	Pro	Pro	Pro	Ser	Gln	Glu	Gly	Pro	Ser	Pro		
		625					630					635					
gct gtg ccc agc atc tac gcc act ctg gcc atc cac tag cccagggggg 2272																	
Ala	Val	Pro	Ser	Ile	Tyr	Ala	Thr	Leu	Ala	Ile	His						
	640					645				650							
gacgcagacc ccacactcca tggagtctgg aatgcatggg agctgcccc ccagtggaca 2332																	
ccattggacc ccaccagcc tggatctacc ccaggagact ctgggaactt ttaggggtca 2392																	
ctcaattctg cagtataaat aactaatgtc tctacaattt tgaataaag caacagactt 2452																	
ctcaataatc aatgaagtag ctgagaaaac taagtcagaa agtgcattaa actgaatcac 2512																	
aatgtaaata ttacacatca agcgatgaaa ctggaaaact acaagccacg aatgaatgaa 2572																	
ttaggaaga aaaaaagtag gaaatgaatg atcttggtt tcctataaga aatttagggc 2632																	
agggcacggt ggctcagcc tgtaattcca gcactttggg aggccgaggc gggcagatca 2692																	
cgagttcagg agatcgagac catcttgcc aacatggtga aacctgtct ctctaaaaa 2752																	
tacaaaaatt agctggatgt ggtggcagtg cctgtaatcc cagctatttg ggaggctgag 2812																	
gcaggagaat cgcttgaacc agggagtcag aggtttcagt gagccaagat cgcaccactg 2872																	
ctctccagcc tggcgacaag caggctgtct cgttcagtc gacggcccat 2922																	

<210> SEQ ID NO 2

<211> LENGTH: 650

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

Met	Thr	Pro	Ile	Leu	Thr	Val	Leu	Ile	Cys	Leu	Gly	Leu	Ser	Leu	Gly		
1				5					10					15			
Pro	Arg	Thr	His	Val	Gln	Ala	Gly	His	Leu	Pro	Lys	Pro	Thr	Leu	Trp		
			20					25					30				
Ala	Glu	Pro	Gly	Ser	Val	Ile	Thr	Gln	Gly	Ser	Pro	Val	Thr	Leu	Arg		
		35					40					45					
Cys	Gln	Gly	Gly	Gln	Glu	Thr	Gln	Glu	Tyr	Arg	Leu	Tyr	Arg	Glu	Lys		
	50				55					60							
Lys	Thr	Ala	Pro	Trp	Ile	Thr	Arg	Ile	Pro	Gln	Glu	Leu	Val	Lys	Lys		
65				70					75					80			
Gly	Gln	Phe	Pro	Ile	Pro	Ser	Ile	Thr	Trp	Glu	His	Ala	Gly	Arg	Tyr		
			85					90						95			
Arg	Cys	Tyr	Tyr	Gly	Ser	Asp	Thr	Ala	Gly	Arg	Ser	Glu	Ser	Ser	Asp		
		100					105						110				
Pro	Leu	Glu	Leu	Val	Val	Thr	Gly	Ala	Tyr	Ile	Lys	Pro	Thr	Leu	Ser		
	115					120						125					
Ala	Gln	Pro	Ser	Pro	Val	Val	Asn	Ser	Gly	Gly	Asn	Val	Thr	Leu	Gln		
	130				135						140						
Cys	Asp	Ser	Gln	Val	Ala	Phe	Asp	Gly	Phe	Ile	Leu	Cys	Lys	Glu	Gly		
145				150					155					160			
Glu	Asp	Glu	His	Pro	Gln	Cys	Leu	Asn	Ser	Gln	Pro	His	Ala	Arg	Gly		
			165					170						175			
Ser	Ser	Arg	Ala	Ile	Phe	Ser	Val	Gly	Pro	Val	Ser	Pro	Ser	Arg	Arg		

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180					185					190					
Trp	Trp	Tyr	Arg	Cys	Tyr	Ala	Tyr	Asp	Ser	Asn	Ser	Pro	Tyr	Glu	Trp
		195					200					205			
Ser	Leu	Pro	Ser	Asp	Leu	Leu	Glu	Leu	Leu	Val	Leu	Gly	Val	Ser	Lys
	210					215						220			
Lys	Pro	Ser	Leu	Ser	Val	Gln	Pro	Gly	Pro	Ile	Val	Ala	Pro	Glu	Glu
225					230					235					240
Thr	Leu	Thr	Leu	Gln	Cys	Gly	Ser	Asp	Ala	Gly	Tyr	Asn	Arg	Phe	Val
				245					250					255	
Leu	Tyr	Lys	Asp	Gly	Glu	Arg	Asp	Phe	Leu	Gln	Leu	Ala	Gly	Ala	Gln
			260					265						270	
Pro	Gln	Ala	Gly	Leu	Ser	Gln	Ala	Asn	Phe	Thr	Leu	Gly	Pro	Val	Ser
		275					280						285		
Arg	Ser	Tyr	Gly	Gly	Gln	Tyr	Arg	Cys	Tyr	Gly	Ala	His	Asn	Leu	Ser
	290					295						300			
Ser	Glu	Trp	Ser	Ala	Pro	Ser	Asp	Pro	Leu	Asp	Ile	Leu	Ile	Ala	Gly
305					310					315					320
Gln	Phe	Tyr	Asp	Arg	Val	Ser	Leu	Ser	Val	Gln	Pro	Gly	Pro	Thr	Val
				325					330					335	
Ala	Ser	Gly	Glu	Asn	Val	Thr	Leu	Leu	Cys	Gln	Ser	Gln	Gly	Trp	Met
			340						345					350	
Gln	Thr	Phe	Leu	Leu	Thr	Lys	Glu	Gly	Ala	Ala	Asp	Asp	Pro	Trp	Arg
		355					360						365		
Leu	Arg	Ser	Thr	Tyr	Gln	Ser	Gln	Lys	Tyr	Gln	Ala	Glu	Phe	Pro	Met
	370					375						380			
Gly	Pro	Val	Thr	Ser	Ala	His	Ala	Gly	Thr	Tyr	Arg	Cys	Tyr	Gly	Ser
385					390					395					400
Gln	Ser	Ser	Lys	Pro	Tyr	Leu	Leu	Thr	His	Pro	Ser	Asp	Pro	Leu	Glu
				405					410					415	
Leu	Val	Val	Ser	Gly	Pro	Ser	Gly	Gly	Pro	Ser	Ser	Pro	Thr	Thr	Gly
			420					425						430	
Pro	Thr	Ser	Thr	Ser	Gly	Pro	Glu	Asp	Gln	Pro	Leu	Thr	Pro	Thr	Gly
		435					440						445		
Ser	Asp	Pro	Gln	Ser	Gly	Leu	Gly	Arg	His	Leu	Gly	Val	Val	Ile	Gly
	450					455						460			
Ile	Leu	Val	Ala	Val	Ile	Leu	Phe								
465					470					475					480
Leu	Ile	Leu	Arg	His	Arg	Arg	Gln	Gly	Lys	His	Trp	Thr	Ser	Thr	Gln
				485					490					495	
Arg	Lys	Ala	Asp	Phe	Gln	His	Pro	Ala	Gly	Ala	Val	Gly	Pro	Glu	Pro
			500					505						510	
Thr	Asp	Arg	Gly	Leu	Gln	Trp	Arg	Ser	Ser	Pro	Ala	Ala	Asp	Ala	Gln
		515					520						525		
Glu	Glu	Asn	Leu	Tyr	Ala	Ala	Val	Lys	His	Thr	Gln	Pro	Glu	Asp	Gly
	530					535						540			
Val	Glu	Met	Asp	Thr	Arg	Ser	Pro	His	Asp	Glu	Asp	Pro	Gln	Ala	Val
545					550					555					560
Thr	Tyr	Ala	Glu	Val	Lys	His	Ser	Arg	Pro	Arg	Arg	Glu	Met	Ala	Ser
				565					570					575	
Pro	Pro	Ser	Pro	Leu	Ser	Gly	Glu	Phe	Leu	Asp	Thr	Lys	Asp	Arg	Gln
			580					585						590	
Ala	Glu	Glu	Asp	Arg	Gln	Met	Asp	Thr	Glu	Ala	Ala	Ala	Ser	Glu	Ala
		595					600						605		

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Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg
610                               615                               620

Lys Ala Thr Glu Pro Pro Ser Gln Glu Gly Pro Ser Pro Ala Val
625                               630                               635                               640

Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
                               645                               650

<210> SEQ ID NO 3
<211> LENGTH: 2777
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (168)..(2126)

<400> SEQUENCE: 3

agctcagcct ggggggcaca gccagatgcy agatgcgtct ctgctgatct gagtctgcct      60
gcagcatgga cctgggtctt ccctgaagca tctccagggc tggagggacg actgccatgc      120
accgagggct catccatcca cagagcaggg cagtgggagg agacgcc atg acc ccc      176
                               Met Thr Pro
                               1
atc ctc acg gtc ctg atc tgt ctc ggg ctg agt ctg ggc ccc agg acc      224
Ile Leu Thr Val Leu Ile Cys Leu Gly Leu Ser Leu Gly Pro Arg Thr
5                               10                               15
cac gtg cag gca ggg cac ctc ccc aag ccc acc ctc tgg gct gaa cca      272
His Val Gln Ala Gly His Leu Pro Lys Pro Thr Leu Trp Ala Glu Pro
20                               25                               30                               35
ggc tct gtg atc acc cag ggg agt cct gtg acc ctc agg tgt cag ggg      320
Gly Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu Arg Cys Gln Gly
40                               45                               50
ggc cag gag acc cag gag tac cgt cta tat aga gaa aag aaa aca gca      368
Gly Gln Glu Thr Gln Glu Tyr Arg Leu Tyr Arg Glu Lys Lys Thr Ala
55                               60                               65
ctc tgg att aca cgg atc cca cag gag ctt gtg aag aag ggc cag ttc      416
Leu Trp Ile Thr Arg Ile Pro Gln Glu Leu Val Lys Lys Gly Gln Phe
70                               75                               80
ccc atc cca tcc atc acc tgg gaa cat gca ggg cgg tat cgc tgt tac      464
Pro Ile Pro Ser Ile Thr Trp Glu His Ala Gly Arg Tyr Arg Cys Tyr
85                               90                               95
tat ggt agc gac act gca ggc cgc tca gag agc agt gac ccc ctg gag      512
Tyr Gly Ser Asp Thr Ala Gly Arg Ser Glu Ser Ser Asp Pro Leu Glu
100                               105                               110                               115
ctg gtg gtg aca gga gcc tac atc aaa ccc acc ctc tca gcc cag ccc      560
Leu Val Val Thr Gly Ala Tyr Ile Lys Pro Thr Leu Ser Ala Gln Pro
120                               125                               130
agc ccc gtg gtg aac tca gga ggg aat gta atc ctc cag tgt gac tca      608
Ser Pro Val Val Asn Ser Gly Gly Asn Val Ile Leu Gln Cys Asp Ser
135                               140                               145
cag gtg gca ttt gat ggc ttc agt ctg tgt aag gaa gga gaa gat gaa      656
Gln Val Ala Phe Asp Gly Phe Ser Leu Cys Lys Glu Gly Glu Asp Glu
150                               155                               160
cac cca caa tgc ctg aac tcc cag ccc cat gcc cgt ggg tgc tcc cgc      704
His Pro Gln Cys Leu Asn Ser Gln Pro His Ala Arg Gly Ser Ser Arg
165                               170                               175
gcc atc ttc tcc gtg ggc ccc gtg agc ccg agt cgc agg tgg tgg tac      752
Ala Ile Phe Ser Val Gly Pro Val Ser Pro Ser Arg Arg Trp Trp Tyr
180                               185                               190                               195
agg tgc tat gct tat gac tgc aac tct ccc tat gag tgg tct cta ccc      800
Arg Cys Tyr Ala Tyr Asp Ser Asn Ser Pro Tyr Glu Trp Ser Leu Pro

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Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala Gln Glu Glu	
520 525 530	
aac ctc tat gct gcc gtg aag cac aca cag cct gag gat ggg gtg gag	1808
Asn Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu Asp Gly Val Glu	
535 540 545	
atg gac act cgg cag agc cca cac gat gaa gac ccc cag gca gtg acg	1856
Met Asp Thr Arg Gln Ser Pro His Asp Glu Asp Pro Gln Ala Val Thr	
550 555 560	
tat gcc gag gtg aaa cac tcc aga cct agg aga gaa atg gcc tct cct	1904
Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg Glu Met Ala Ser Pro	
565 570 575	
cct tcc cca ctg tct ggg gaa ttc ctg gac aca aag gac aga cag gcg	1952
Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala	
580 585 590 595	
gaa gag gac agg cag atg gac act gag gct gct gca tct gaa gcc ccc	2000
Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Pro	
600 605 610	
cag gat gtg acc tac gcc cag ctg cac agc ttg acc ctc aga cgg gag	2048
Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg Glu	
615 620 625	
gca act gag cct cct cca tcc cag gaa ggg ccc tct cca gct gtg ccc	2096
Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro Ala Val Pro	
630 635 640	
agc atc tac gcc act ctg gcc atc cac tag cccagggggg gacgcagacc	2146
Ser Ile Tyr Ala Thr Leu Ala Ile His	
645 650	
ccacactcca tggagtctgg aatgcatggg agctgcccc ccagtggaca ccattggacc	2206
ccaccagacc tggatctacc ccaggagact ctgggaactt ttaggggtca ctcaattctg	2266
cagtataaat aactaatgtc tctacaattt tgaataaag caatagactt ctcaataatc	2326
aatgaagtag ctgagaaaac taagtcagaa agtgcatata actgaatcac aatgtaaata	2386
ttacacatca agcgatgaaa ctggaaaact acaagccacg aatgaatgaa ttaggaaaga	2446
aaaaaagtag gaaatgaatg atcttggtt tcctataaga aatttagggc agggcacggt	2506
ggctcacgcc tgtaattcca gcaactttggg aggccgaggc gggcagatca cgagttcagg	2566
agatcgagac catcttggcc aacatggtga aacctgtct ctctaaaaa tacaaaaatt	2626
agctggatgt ggtggcagtg cctgtaatcc cagctatttg ggaggtgag gcaggagaat	2686
cgcttgaacc agggagtcag aggtttcagt gagccaagat cgcaccactg ctctccagcc	2746
tggcgacaga gggagactcc atctcaaatt a	2777

<210> SEQ ID NO 4

<211> LENGTH: 652

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

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Pro Arg Thr His Val Gln Ala Gly His Leu Pro Lys Pro Thr Leu Trp	
20 25 30	
Ala Glu Pro Gly Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu Arg	
35 40 45	
Cys Gln Gly Gly Gln Glu Thr Gln Glu Tyr Arg Leu Tyr Arg Glu Lys	
50 55 60	
Lys Thr Ala Leu Trp Ile Thr Arg Ile Pro Gln Glu Leu Val Lys Lys	
65 70 75 80	

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Gly Gln Phe Pro Ile Pro Ser Ile Thr Trp Glu His Ala Gly Arg Tyr
 85 90 95

Arg Cys Tyr Tyr Gly Ser Asp Thr Ala Gly Arg Ser Glu Ser Ser Asp
 100 105 110

Pro Leu Glu Leu Val Val Thr Gly Ala Tyr Ile Lys Pro Thr Leu Ser
 115 120 125

Ala Gln Pro Ser Pro Val Val Asn Ser Gly Gly Asn Val Ile Leu Gln
 130 135 140

Cys Asp Ser Gln Val Ala Phe Asp Gly Phe Ser Leu Cys Lys Glu Gly
 145 150 155 160

Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His Ala Arg Gly
 165 170 175

Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Ser Arg Arg
 180 185 190

Trp Trp Tyr Arg Cys Tyr Ala Tyr Asp Ser Asn Ser Pro Tyr Glu Trp
 195 200 205

Ser Leu Pro Ser Asp Leu Leu Glu Leu Leu Val Leu Gly Val Ser Lys
 210 215 220

Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Ile Val Ala Pro Glu Glu
 225 230 235 240

Thr Leu Thr Leu Gln Cys Gly Ser Asp Ala Gly Tyr Asn Arg Phe Val
 245 250 255

Leu Tyr Lys Asp Gly Glu Arg Asp Phe Leu Gln Leu Ala Gly Ala Gln
 260 265 270

Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser
 275 280 285

Arg Ser Tyr Gly Gly Gln Tyr Arg Cys Tyr Gly Ala His Asn Leu Ser
 290 295 300

Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Ala Gly
 305 310 315 320

Gln Phe Tyr Asp Arg Val Ser Leu Ser Val Gln Pro Gly Pro Thr Val
 325 330 335

Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Gln Gly Trp Met
 340 345 350

Gln Thr Phe Leu Leu Thr Lys Glu Gly Ala Ala Asp Asp Pro Trp Arg
 355 360 365

Leu Arg Ser Thr Tyr Gln Ser Gln Lys Tyr Gln Ala Glu Phe Pro Met
 370 375 380

Gly Pro Val Thr Ser Ala His Ala Gly Thr Tyr Arg Cys Tyr Gly Ser
 385 390 395 400

Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser Asp Pro Leu Glu
 405 410 415

Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro Thr Thr Gly
 420 425 430

Pro Thr Ser Thr Ser Ala Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr
 435 440 445

Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val Val Ile
 450 455 460

Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu Leu Leu
 465 470 475 480

Phe Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp Thr Ser Thr
 485 490 495

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Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val Gly Pro Glu
 500 505 510
 Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala
 515 520 525
 Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu Asp
 530 535 540
 Gly Val Glu Met Asp Thr Arg Gln Ser Pro His Asp Glu Asp Pro Gln
 545 550 555 560
 Ala Val Thr Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg Glu Met
 565 570 575
 Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp
 580 585 590
 Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser
 595 600 605
 Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu
 610 615 620
 Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro
 625 630 635 640
 Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
 645 650

<210> SEQ ID NO 5
 <211> LENGTH: 30
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

tatgtcgacc atgaccccca tcctcaccgt 30

<210> SEQ ID NO 6
 <211> LENGTH: 52
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

tatgggtctt gctccaggag aagatcttcc ttctataacc cccaggtgcc tt 52

<210> SEQ ID NO 7
 <211> LENGTH: 1605
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (93)..(1412)

<400> SEQUENCE: 7

gagcctccaa gtgtccacac cctgtgtgtc ctctgtctg ccagcacoga gggctcatec 60

atccacagag cagtgcagtg ggaggagacg cc atg acc ccc atc ctc acg gtc 113
 Met Thr Pro Ile Leu Thr Val
 1 5

ctg atc tgt ctc ggg ctg agc ctg gac ccc agg acc cac gtg cag gca 161
 Leu Ile Cys Leu Gly Leu Ser Leu Asp Pro Arg Thr His Val Gln Ala
 10 15 20

ggg ccc ctc ccc aag ccc acc ctc tgg gct gag cca ggc tct gtg atc 209
 Gly Pro Leu Pro Lys Pro Thr Leu Trp Ala Glu Pro Gly Ser Val Ile
 25 30 35

acc caa ggg agt cct gtg acc ctc agg tgt cag ggg agc ctg gag acg 257
 Thr Gln Gly Ser Pro Val Thr Leu Arg Cys Gln Gly Ser Leu Glu Thr
 40 45 50 55

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cag gag tac cat cta tat aga gaa aag aaa aca gca ctc tgg att aca Gln Glu Tyr His Leu Tyr Arg Glu Lys Lys Thr Ala Leu Trp Ile Thr 60 65 70	305
cgg atc cca cag gag ctt gtg aag aag ggc cag ttc ccc atc cta tcc Arg Ile Pro Gln Glu Leu Val Lys Lys Gly Gln Phe Pro Ile Leu Ser 75 80 85	353
atc acc tgg gaa cat gca ggg cgg tat tgc tgt atc tat ggc agc cac Ile Thr Trp Glu His Ala Gly Arg Tyr Cys Cys Ile Tyr Gly Ser His 90 95 100	401
act gca ggc ctc tca gag agc agt gac ccc ctg gag ctg gtg gtg aca Thr Ala Gly Leu Ser Glu Ser Ser Asp Pro Leu Glu Leu Val Val Thr 105 110 115	449
gga gcc tac agc aaa ccc acc ctc tca gct ctg ccc agc cct gtg gtg Gly Ala Tyr Ser Lys Pro Thr Leu Ser Ala Leu Pro Ser Pro Val Val 120 125 130 135	497
acc tca gga agg aat gtg acc atc cag tgt gac tca cag gtg gca ttt Thr Ser Gly Arg Asn Val Thr Ile Gln Cys Asp Ser Gln Val Ala Phe 140 145 150	545
gat ggc ttc att ctg tgt aag gaa gga gaa gat gaa cac cca caa tgc Asp Gly Phe Ile Leu Cys Lys Glu Gly Glu Asp Glu His Pro Gln Cys 155 160 165	593
ctg aac tcc cat tcc cat gcc cgt ggg tca tcc cgg gcc atc ttc tcc Leu Asn Ser His Ser His Ala Arg Gly Ser Ser Arg Ala Ile Phe Ser 170 175 180	641
gtg ggc ccc gtg agc cca agt cgc agg tgg tcg tac agg tgc tat ggt Val Gly Pro Val Ser Pro Ser Arg Arg Trp Ser Tyr Arg Cys Tyr Gly 185 190 195	689
tat gac tcg cgc gct ccc tat gtg tgg tct cta ccc agt gat ctc ctg Tyr Asp Ser Arg Ala Pro Tyr Val Trp Ser Leu Pro Ser Asp Leu Leu 200 205 210 215	737
ggg ctc ctg gtc cca ggt gtt tct aag aag cca tca ctc tca gtg cag Gly Leu Leu Val Pro Gly Val Ser Lys Lys Pro Ser Leu Ser Val Gln 220 225 230	785
ccg ggt cct gtc gtg gcc cct ggg gag aag ctg acc ttc cag tgt ggc Pro Gly Pro Val Val Ala Pro Gly Glu Lys Leu Thr Phe Gln Cys Gly 235 240 245	833
tct gat gcc ggc tac gac aga ttt gtt ctg tac aag gag tgg gga cgt Ser Asp Ala Gly Tyr Asp Arg Phe Val Leu Tyr Lys Glu Trp Gly Arg 250 255 260	881
gac ttc ctc cag cgc cct ggc cgg cag ccc cag gct ggg ctc tcc cag Asp Phe Leu Gln Arg Pro Gly Arg Gln Pro Gln Ala Gly Leu Ser Gln 265 270 275	929
gcc aac ttc acc ctg ggc cct gtg agc cgc tcc tac ggg ggc cag tac Ala Asn Phe Thr Leu Gly Pro Val Ser Arg Ser Tyr Gly Gly Gln Tyr 280 285 290 295	977
aca tgc tcc ggt gca tac aac ctc tcc tcc gag tgg tcg gcc ccc agc Thr Cys Ser Gly Ala Tyr Asn Leu Ser Ser Glu Trp Ser Ala Pro Ser 300 305 310	1025
gac ccc ctg gac atc ctg atc aca gga cag atc cgt gcc aga ccc ttc Asp Pro Leu Asp Ile Leu Ile Thr Gly Gln Ile Arg Ala Arg Pro Phe 315 320 325	1073
ctc tcc gtg cgg cgg ggc ccc aca gtg gcc tca gga gag aac gtg acc Leu Ser Val Arg Pro Gly Pro Thr Val Ala Ser Gly Glu Asn Val Thr 330 335 340	1121
ctg ctg tgt cag tca cag gga ggg atg cac act ttc ctt ttg acc aag Leu Leu Cys Gln Ser Gln Gly Gly Met His Thr Phe Leu Leu Thr Lys 345 350 355	1169
gag ggg gca gct gat tcc ccg ctg cgt cta aaa tca aag cgc caa tct Glu Gly Ala Ala Asp Ser Pro Leu Arg Leu Lys Ser Lys Arg Gln Ser 360 365 370 375	1217

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cat aag tac cag gct gaa ttc ccc atg agt cct gtg acc tcg gcc cac 1265
His Lys Tyr Gln Ala Glu Phe Pro Met Ser Pro Val Thr Ser Ala His
      380                               385                               390

gcg ggg acc tac agg tgc tac ggc tca ctc agc tcc aac ccc tac ctg 1313
Ala Gly Thr Tyr Arg Cys Tyr Gly Ser Leu Ser Ser Asn Pro Tyr Leu
      395                               400                               405

ctg act cac ccc agt gac ccc ctg gag ctc gtg gtc tca gga gca gct 1361
Leu Thr His Pro Ser Asp Pro Leu Glu Leu Val Val Ser Gly Ala Ala
      410                               415                               420

gag acc ctc agc cca cca caa aac aag tcc gac tcc aag gct ggt gag 1409
Glu Thr Leu Ser Pro Pro Gln Asn Lys Ser Asp Ser Lys Ala Gly Glu
      425                               430                               435

tga ggagatgctt gccgtgatga cgctgggcac agagggtcag gtctgtcaa 1462

gaggagctgg gtgtctctgg tggacatttg aagaattata ttcattccaa cttgaagaat 1522

tattcaacac cttaacaat gtatatgtga agtactttat tctttcatat tttaaaaata 1582

aaagataatt atccatgaga aaa 1605

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<210> SEQ ID NO 8
<211> LENGTH: 439
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 8

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Met Thr Pro Ile Leu Thr Val Leu Ile Cys Leu Gly Leu Ser Leu Asp
1           5           10          15

Pro Arg Thr His Val Gln Ala Gly Pro Leu Pro Lys Pro Thr Leu Trp
      20           25           30

Ala Glu Pro Gly Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu Arg
      35           40           45

Cys Gln Gly Ser Leu Glu Thr Gln Glu Tyr His Leu Tyr Arg Glu Lys
      50           55           60

Lys Thr Ala Leu Trp Ile Thr Arg Ile Pro Gln Glu Leu Val Lys Lys
      65           70           75           80

Gly Gln Phe Pro Ile Leu Ser Ile Thr Trp Glu His Ala Gly Arg Tyr
      85           90           95

Cys Cys Ile Tyr Gly Ser His Thr Ala Gly Leu Ser Glu Ser Ser Asp
      100          105          110

Pro Leu Glu Leu Val Val Thr Gly Ala Tyr Ser Lys Pro Thr Leu Ser
      115          120          125

Ala Leu Pro Ser Pro Val Val Thr Ser Gly Arg Asn Val Thr Ile Gln
      130          135          140

Cys Asp Ser Gln Val Ala Phe Asp Gly Phe Ile Leu Cys Lys Glu Gly
      145          150          155          160

Glu Asp Glu His Pro Gln Cys Leu Asn Ser His Ser His Ala Arg Gly
      165          170          175

Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Ser Arg Arg
      180          185          190

Trp Ser Tyr Arg Cys Tyr Gly Tyr Asp Ser Arg Ala Pro Tyr Val Trp
      195          200          205

Ser Leu Pro Ser Asp Leu Leu Gly Leu Leu Val Pro Gly Val Ser Lys
      210          215          220

Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Val Val Ala Pro Gly Glu
      225          230          235          240

Lys Leu Thr Phe Gln Cys Gly Ser Asp Ala Gly Tyr Asp Arg Phe Val

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tat ggc tgt cag tat tac agc cgc gct cgg tgg tct gag ctc agt gac	516
Tyr Gly Cys Gln Tyr Tyr Ser Arg Ala Arg Trp Ser Glu Leu Ser Asp	
100 105 110	
ccc ctg gtg ctg gtg atg aca gga gcc tac cca aaa ccc acc ctc tca	564
Pro Leu Val Leu Val Met Thr Gly Ala Tyr Pro Lys Pro Thr Leu Ser	
115 120 125	
gcc cag ccc agc cct gtg gtg acc tca gga gga agg gtg acc ctc cag	612
Ala Gln Pro Ser Pro Val Val Thr Ser Gly Gly Arg Val Thr Leu Gln	
130 135 140	
tgt gag tca cag gtg gca ttt ggc ggc ttc att ctg tgt aag gaa gga	660
Cys Glu Ser Gln Val Ala Phe Gly Gly Phe Ile Leu Cys Lys Glu Gly	
145 150 155	
gaa gat gaa cac cca caa tgc ctg aac tcc cag ccc cat gcc cgt ggg	708
Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His Ala Arg Gly	
160 165 170 175	
tcg tcc cgc gcc atc ttc tcc gtg ggc ccc gtg agc ccg aat cgc agg	756
Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Asn Arg Arg	
180 185 190	
tgg tcg cac agg tgc tat ggt tat gac ttg aac tct ccc tat gtg tgg	804
Trp Ser His Arg Cys Tyr Gly Tyr Asp Leu Asn Ser Pro Tyr Val Trp	
195 200 205	
tct tca ccc agt gat ctc ctg gag ctc ctg gtc cca ggt gtt tct aag	852
Ser Ser Pro Ser Asp Leu Leu Leu Leu Val Pro Gly Val Ser Lys	
210 215 220	
aag cca tca ctc tca gtg cag ccg ggt cct gtc gtg gcc cct ggg gaa	900
Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Val Val Ala Pro Gly Glu	
225 230 235	
agc ctg acc ctc cag tgt gtc tct gat gtc ggc tat gac aga ttt gtt	948
Ser Leu Thr Leu Gln Cys Val Ser Asp Val Gly Tyr Asp Arg Phe Val	
240 245 250 255	
ctg tac aag gag ggg gaa cgt gac ctt cgc cag ctc cct gcc cgg cag	996
Leu Tyr Lys Glu Gly Glu Arg Asp Leu Arg Gln Leu Pro Gly Arg Gln	
260 265 270	
ccc cag gct ggg ctc tcc cag gcc aac ttc acc ctg ggc cct gtg agc	1044
Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser	
275 280 285	
cgc tcc tac ggg ggc cag tac aga tgc tac ggt gca tac aac ctc tcc	1092
Arg Ser Tyr Gly Gly Gln Tyr Arg Cys Tyr Gly Ala Tyr Asn Leu Ser	
290 295 300	
tcc gag tgg tcg gcc ccc agc gac ccc ctg gac atc ctg atc aca gga	1140
Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Thr Gly	
305 310 315	
cag atc cat ggc aca ccc ttc atc tca gtg cag cca ggc ccc aca gtg	1188
Gln Ile His Gly Thr Pro Phe Ile Ser Val Gln Pro Gly Pro Thr Val	
320 325 330 335	
gcc tca gga gag aac gtg acc ctg ctg tgt cag tca tgg cgg cag ttc	1236
Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Trp Arg Gln Phe	
340 345 350	
cac act ttc ctt ctg acc aag gcg gga gca gct gat gcc cca ctc cgt	1284
His Thr Phe Leu Leu Thr Lys Ala Gly Ala Ala Asp Ala Pro Leu Arg	
355 360 365	
cta aga tca ata cac gaa tat cct aag tac cag gct gaa ttc ccc atg	1332
Leu Arg Ser Ile His Glu Tyr Pro Lys Tyr Gln Ala Glu Phe Pro Met	
370 375 380	
agt cct gtg acc tca gcc cac gcg ggg acc tac agg tgc tac gcc tca	1380
Ser Pro Val Thr Ser Ala His Ala Gly Thr Tyr Arg Cys Tyr Gly Ser	
385 390 395	
ctc aac tcc gac ccc tac ctg ctg tct cac ccc agt gag ccc ctg gag	1428
Leu Asn Ser Asp Pro Tyr Leu Leu Ser His Pro Ser Glu Pro Leu Glu	
400 405 410 415	

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ctc gtg gtc tca gga ccc tcc atg ggt tcc agc ccc cca ccc acc ggt 1476
Leu Val Val Ser Gly Pro Ser Met Gly Ser Ser Pro Pro Pro Thr Gly
      420      425      430

ccc atc tcc aca cct gca ggc cct gag gac cag ccc ctc acc ccc act 1524
Pro Ile Ser Thr Pro Ala Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr
      435      440      445

ggg tcg gat ccc caa agt ggt ctg gga agg cac ctg ggg gtt gtg atc 1572
Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val Val Ile
      450      455      460

ggc atc ttg gtg gcc gtc gtc cta ctg ctc ctc ctc ctc ctc ctc 1620
Gly Ile Leu Val Ala Val Val Leu Leu Leu Leu Leu Leu Leu Leu
      465      470      475

ttc ctc atc ctc cga cat cga cgt cag ggc aaa cac tgg aca tcg acc 1668
Phe Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp Thr Ser Thr
      480      485      490      495

cag aga aag gct gat ttc caa cat cct gca ggg gct gtg ggg cca gag 1716
Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val Gly Pro Glu
      500      505      510

ccc aca gac aga ggc ctg cag tgg agg tcc agc cca gct gcc gac gcc 1764
Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala
      515      520      525

cag gaa gaa aac ctc tat gct gcc gtg aag gac aca cag cct gaa gat 1812
Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys Asp Thr Gln Pro Glu Asp
      530      535      540

ggg gtg gag atg gac act cgg gct gct gca tct gaa gcc ccc cag gat 1860
Gly Val Glu Met Asp Thr Arg Ala Ala Ala Ser Glu Ala Pro Gln Asp
      545      550      555

gtg acc tac gcc cag ctg cac agc ttg acc ctc aga cgg aag gca act 1908
Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg Lys Ala Thr
      560      565      570      575

gag cct cct cca tcc cag gaa agg gaa cct cca gct gag ccc agc atc 1956
Glu Pro Pro Pro Ser Gln Glu Arg Glu Pro Pro Ala Glu Pro Ser Ile
      580      585      590

tac gcc acc ctg gcc atc cac tag cccggagggt acgcagactc cacactcagt 2010
Tyr Ala Thr Leu Ala Ile His
      595

agaaggagac tcaggactgc tgaaggcacg ggagctgccc ccagtggaca ccaatgaacc 2070

ccagtcagcc tggaccacct acaaagacca tgaggagatg ctgggaactt tgggactcac 2130

ttgattctgc agtcgaaata actaatatcc ctacattttt taattaaagc aacagacttc 2190

tcaataaaaag caggtcgtct cgttccaatc t 2221

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<210> SEQ ID NO 10

<211> LENGTH: 598

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

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Met Thr Pro Ile Val Thr Val Leu Ile Cys Leu Gly Leu Ser Leu Gly
1      5      10      15

Pro Arg Thr His Val Gln Thr Gly Thr Ile Pro Lys Pro Thr Leu Trp
      20      25      30

Ala Glu Pro Asp Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu Ser
      35      40      45

Cys Gln Gly Ser Leu Glu Ala Gln Glu Tyr Arg Leu Tyr Arg Glu Lys
      50      55      60

Lys Ser Ala Ser Trp Ile Thr Arg Ile Arg Pro Glu Leu Val Lys Asn
65      70      75      80

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Gly Gln Phe His Ile Pro Ser Ile Thr Trp Glu His Thr Gly Arg Tyr
 85 90 95
 Gly Cys Gln Tyr Tyr Ser Arg Ala Arg Trp Ser Glu Leu Ser Asp Pro
 100 105 110
 Leu Val Leu Val Met Thr Gly Ala Tyr Pro Lys Pro Thr Leu Ser Ala
 115 120 125
 Gln Pro Ser Pro Val Val Thr Ser Gly Gly Arg Val Thr Leu Gln Cys
 130 135 140
 Glu Ser Gln Val Ala Phe Gly Gly Phe Ile Leu Cys Lys Glu Gly Glu
 145 150 155 160
 Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His Ala Arg Gly Ser
 165 170 175
 Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Asn Arg Arg Trp
 180 185 190
 Ser His Arg Cys Tyr Gly Tyr Asp Leu Asn Ser Pro Tyr Val Trp Ser
 195 200 205
 Ser Pro Ser Asp Leu Leu Glu Leu Leu Val Pro Gly Val Ser Lys Lys
 210 215 220
 Pro Ser Leu Ser Val Gln Pro Gly Pro Val Val Ala Pro Gly Glu Ser
 225 230 235 240
 Leu Thr Leu Gln Cys Val Ser Asp Val Gly Tyr Asp Arg Phe Val Leu
 245 250 255
 Tyr Lys Glu Gly Glu Arg Asp Leu Arg Gln Leu Pro Gly Arg Gln Pro
 260 265 270
 Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser Arg
 275 280 285
 Ser Tyr Gly Gly Gln Tyr Arg Cys Tyr Gly Ala Tyr Asn Leu Ser Ser
 290 295 300
 Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Thr Gly Gln
 305 310 315 320
 Ile His Gly Thr Pro Phe Ile Ser Val Gln Pro Gly Pro Thr Val Ala
 325 330 335
 Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Trp Arg Gln Phe His
 340 345 350
 Thr Phe Leu Leu Thr Lys Ala Gly Ala Ala Asp Ala Pro Leu Arg Leu
 355 360 365
 Arg Ser Ile His Glu Tyr Pro Lys Tyr Gln Ala Glu Phe Pro Met Ser
 370 375 380
 Pro Val Thr Ser Ala His Ala Gly Thr Tyr Arg Cys Tyr Gly Ser Leu
 385 390 395 400
 Asn Ser Asp Pro Tyr Leu Leu Ser His Pro Ser Glu Pro Leu Glu Leu
 405 410 415
 Val Val Ser Gly Pro Ser Met Gly Ser Ser Pro Pro Pro Thr Gly Pro
 420 425 430
 Ile Ser Thr Pro Ala Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly
 435 440 445
 Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val Val Ile Gly
 450 455 460
 Ile Leu Val Ala Val Val Leu Leu Leu Leu Leu Leu Leu Leu Phe
 465 470 475 480
 Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp Thr Ser Thr Gln
 485 490 495

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gaa cac cca caa tgc ctg aac tca cag ccc cgt acc cat ggg tgg tcc	704
Glu His Pro Gln Cys Leu Asn Ser Gln Pro Arg Thr His Gly Trp Ser	
165 170 175	
cgg gcc atc ttc tct gtg ggc ccc gtg agc ccg agt cgc agg tgg tcg	752
Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Ser Arg Arg Trp Ser	
180 185 190	
tac agg tgc tat gct tat gac tcg aac tct ccc cat gtg tgg tct cta	800
Tyr Arg Cys Tyr Ala Tyr Asp Ser Asn Ser Pro His Val Trp Ser Leu	
195 200 205 210	
ccc agt gat ctc ctg gag ctc ctg gtc cca gga gca gct gag acc ctc	848
Pro Ser Asp Leu Leu Glu Leu Leu Val Pro Gly Ala Ala Glu Thr Leu	
215 220 225	
agc cca cca caa aac aag tcc gat tcc aag gct gga gca gct aac acc	896
Ser Pro Pro Gln Asn Lys Ser Asp Ser Lys Ala Gly Ala Ala Asn Thr	
230 235 240	
ctc agc cca tca caa aac aag act gcc tca cac ccc cag gat tac aca	944
Leu Ser Pro Ser Gln Asn Lys Thr Ala Ser His Pro Gln Asp Tyr Thr	
245 250 255	
gtg gag aat ctc atc cgc atg ggc ata gct ggc ttg gtc ctg gtg gtc	992
Val Glu Asn Leu Ile Arg Met Gly Ile Ala Gly Leu Val Leu Val Val	
260 265 270	
ctc ggg att ctg cta ttt gag gct cag cac agc cag aga agc ctc tga	1040
Leu Gly Ile Leu Leu Phe Glu Ala Gln His Ser Gln Arg Ser Leu	
275 280 285	
gatgcagccg ggagggtgaac agcagagaga agaatgtacc cttcagagtg gtggagcctt	1100
gggaacagat ctgatgatgc caggagggtc cgggagacaa tttagggtctg atgctatctg	1160
gactgtctgc caatcatttt tagagggagg aatcagtggt ggattgcaga gacattttct	1220
ggagtgatcc atgaaggacc attaacatgt gatacctttc ctctctatta atgttgactt	1280
cccttggttg gatcctcttc tttccccacc cccagacaga catgaggcta catcccacat	1340
ggcagcgttg ggtccacacc tctgcacatc tgtgtgctct ggtccatggt gtgtaacaca	1400
gtcttcttta ttactcattg ccatactccc tgggtgtgctt tactgagcct ccatctcttc	1460
aattcagagt tccaaacgtg cttcagtaac taaatcaatg ggagagtatc ggatttcaac	1520
caggaaaaga taaatccacc ctgatgcctt gacaccctct ctgaaacctc cgagcccttc	1580
ctcctctctc acatgctacc tgtgcagctt ctcttagat cattgtgtaa ccatcactgc	1640
catctgttcc cacacatggt catcacccca caccattca gcagccactc cccattccct	1700
cttccctcca gcacctgcta accacaaatg tgctttctgt ctctacggat ttgcctatc	1760
tgtctgaaaa catttcaate tcctttgacc tgtgagctcc tcacttcgag acttctcgcc	1820
tttcaggcca gaaccaaagt acaccacgtc aaaagcaatg ataggcattt gcagtgtggt	1880
ggtgatccac gaaaggaaaa tcacggaagc aggatagaaa tccagctgca gacaagacct	1940
caggctgatg aatcttgaca agcagttgag ctgttttttt ctactcaoct aggacagtca	2000
ggcagaagta tgcaaaatga ctggggctga ttcttttctg aattgtcgca aacagcaaga	2060
ggacttgagt cctagcatta aagagttcaa catgtctagg tccaagacca ctgttggtgtt	2120
tgaaggatgt aaaacctctc tgcataggat ggaatatttg gagggaggat cctgaaaaac	2180
atgagggatc aaatagtctc caactttcta ggacaaaggg agcagctatt tgccatctac	2240
cttcagaat aaagaaatct tatcattcac catctacct ctagaataaa gaaatcttat	2300
cattcgccat ctaccctgta gaataagaa atcttatcat tcaccgtcta cctctagag	2360
taaacaaatc ttatcattca ccatctaccc tctagaataa agaaatctta tcattcgcca	2420

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tctaccctct agaataaaga aatctt

2446

<210> SEQ ID NO 12
 <211> LENGTH: 289
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

Met Thr Pro Ile Leu Thr Val Leu Ile Cys Leu Gly Leu Ser Leu Gly
 1 5 10 15
 Pro Arg Thr His Val Gln Ala Gly Thr Leu Pro Lys Pro Thr Leu Trp
 20 25 30
 Ala Glu Pro Gly Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu Trp
 35 40 45
 Cys Gln Gly Ile Leu Glu Thr Gln Glu Tyr Arg Leu Tyr Arg Glu Lys
 50 55 60
 Lys Thr Ala Pro Trp Ile Thr Arg Ile Pro Gln Glu Ile Val Lys Lys
 65 70 75 80
 Gly Gln Phe Pro Ile Pro Ser Ile Thr Trp Glu His Thr Gly Arg Tyr
 85 90 95
 Arg Cys Phe Tyr Gly Ser His Thr Ala Gly Trp Ser Glu Pro Ser Asp
 100 105 110
 Pro Leu Glu Leu Val Val Thr Gly Ala Tyr Ile Lys Pro Thr Leu Ser
 115 120 125
 Ala Leu Pro Ser Pro Val Val Thr Ser Gly Gly Asn Val Thr Leu His
 130 135 140
 Cys Val Ser Gln Val Ala Phe Gly Ser Phe Ile Leu Cys Lys Glu Gly
 145 150 155 160
 Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro Arg Thr His Gly
 165 170 175
 Trp Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Ser Arg Arg
 180 185 190
 Trp Ser Tyr Arg Cys Tyr Ala Tyr Asp Ser Asn Ser Pro His Val Trp
 195 200 205
 Ser Leu Pro Ser Asp Leu Leu Glu Leu Leu Val Pro Gly Ala Ala Glu
 210 215 220
 Thr Leu Ser Pro Pro Gln Asn Lys Ser Asp Ser Lys Ala Gly Ala Ala
 225 230 235 240
 Asn Thr Leu Ser Pro Ser Gln Asn Lys Thr Ala Ser His Pro Gln Asp
 245 250 255
 Tyr Thr Val Glu Asn Leu Ile Arg Met Gly Ile Ala Gly Leu Val Leu
 260 265 270
 Val Val Leu Gly Ile Leu Leu Phe Glu Ala Gln His Ser Gln Arg Ser
 275 280 285

Leu

<210> SEQ ID NO 13
 <211> LENGTH: 1910
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (183)..(1652)

<400> SEQUENCE: 13

ctcactgccacacgcagctcaacctgagctacacagccagatgcgagatgcttctctgct

60

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gatctgagtc tgctgcagc atggacctg gtcttccctg aagcatctcc agggctggag	120
ggacgactgc catgcaccga gggctcatcc atccgcagag cagggcagtg ggaggagacg	180
ct atg acc ccc atc gtc aca gtc ctg atc tgt ctc agg ctg agt ctg Met Thr Pro Ile Val Thr Val Leu Ile Cys Leu Arg Leu Ser Leu 1 5 10 15	227
ggc ccc cgg acc cac gtg cag gca ggg acc ctc ccc aag ccc aca ctc Gly Pro Arg Thr His Val Gln Ala Gly Thr Leu Pro Lys Pro Thr Leu 20 25 30	275
tgg gct gag cca ggc tct gtg atc acc cag ggg agt ccc gtg acc ctc Trp Ala Glu Pro Gly Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu 35 40 45	323
tgg tgt cag ggg atc ctg gag acc cag gag tac cgt ctg tat aga gaa Trp Cys Gln Gly Ile Leu Glu Thr Gln Glu Tyr Arg Leu Tyr Arg Glu 50 55 60	371
aag aaa aca gca ccc tgg att aca cgg atc cca cag gag att gtg aag Lys Lys Thr Ala Pro Trp Ile Thr Arg Ile Pro Gln Glu Ile Val Lys 65 70 75	419
aag ggc cag ttc ccc atc cca tcc atc acc tgg gaa cac aca ggg cgg Lys Gly Gln Phe Pro Ile Pro Ser Ile Thr Trp Glu His Thr Gly Arg 80 85 90 95	467
tat cgc tgt ttc tac ggt agc cac act gca ggc tgg tca gag ccc agt Tyr Arg Cys Phe Tyr Gly Ser His Thr Ala Gly Trp Ser Glu Pro Ser 100 105 110	515
gac ccc ctg gag ctg gtg gtg aca gga gcc tac atc aaa ccc acc ctc Asp Pro Leu Glu Leu Val Val Thr Gly Ala Tyr Ile Lys Pro Thr Leu 115 120 125	563
tca gct cta ccc agc cct gtg gtg acc tca gga ggg aac gtg acc ctc Ser Ala Leu Pro Ser Pro Val Val Thr Ser Gly Gly Asn Val Thr Leu 130 135 140	611
cat tgt gtc tca cag gtg gca ttt ggc agc ttc att ctg tgt aag gaa His Cys Val Ser Gln Val Ala Phe Gly Ser Phe Ile Leu Cys Lys Glu 145 150 155	659
gga gaa gat gaa cac cca caa tgc ctg aac tca cag ccc cgt acc cat Gly Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro Arg Thr His 160 165 170 175	707
ggg tgg tcc cgg gcc atc ttc tct gtg ggc ccc gtg agc ccg agt cgc Gly Trp Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Ser Arg 180 185 190	755
agg tgg tgg tac agg tgc tat gct tat gac tgg aac tct ccc cat gtg Arg Trp Ser Tyr Arg Cys Tyr Ala Tyr Asp Ser Asn Ser Pro His Val 195 200 205	803
tgg tct cta ccc agt gat ctc ctg gag ctc ctg gtc cta ggt gtt tct Trp Ser Leu Pro Ser Asp Leu Leu Glu Leu Leu Val Leu Gly Val Ser 210 215 220	851
aag aag cca tca ctc tca gtg cag cca ggt cct ata gtg gcc cct ggg Lys Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Ile Val Ala Pro Gly 225 230 235	899
gag agc ctg acc ctc cag tgt gtt tct gat gtc agc tac gac aga ttt Glu Ser Leu Thr Leu Gln Cys Val Ser Asp Val Ser Tyr Asp Arg Phe 240 245 250 255	947
gtt ctg tat aag gag gga gaa cgt gac ttc ctc cag ctc cct ggc cca Val Leu Tyr Lys Glu Gly Glu Arg Asp Phe Leu Gln Leu Pro Gly Pro 260 265 270	995
cag ccc cag gct ggg ctc tcc cag gcc aac ttc acc ctg ggc cct gtg Gln Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val 275 280 285	1043
agc cgc tcc tac ggg ggc cag tac aga tgc tcc ggt gca tac aac ctc Ser Arg Ser Tyr Gly Gly Gln Tyr Arg Cys Ser Gly Ala Tyr Asn Leu 290 295 300	1091

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tcc tcc gag tgg tcg gcc ccc agc gac ccc ctg gac atc ctg atc gca	1139
Ser Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Ala	
305 310 315	
gga cag ttc cgt ggc aga ccc ttc atc tcg gtg cat ccg ggc ccc acg	1187
Gly Gln Phe Arg Gly Arg Pro Phe Ile Ser Val His Pro Gly Pro Thr	
320 325 330 335	
gtg gcc tca gga gag aac gtg acc ctg ctg tgt cag tca tgg ggg ccg	1235
Val Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Trp Gly Pro	
340 345 350	
ttc cac act ttc ctt ctg acc aag gcg gga gca gct gat gcc ccc ctc	1283
Phe His Thr Phe Leu Leu Thr Lys Ala Gly Ala Ala Asp Ala Pro Leu	
355 360 365	
cgt ctc aga tca ata cac gaa tat cct aag tac cag gct gaa ttc cct	1331
Arg Leu Arg Ser Ile His Glu Tyr Pro Lys Tyr Gln Ala Glu Phe Pro	
370 375 380	
atg agt cct gtg acc tca gcc cac tcg ggg acc tac agg tgc tac ggc	1379
Met Ser Pro Val Thr Ser Ala His Ser Gly Thr Tyr Arg Cys Tyr Gly	
385 390 395	
tca ctc agc tcc aac ccc tac ctg ctg tct cac ccc agt gac tcc ctg	1427
Ser Leu Ser Ser Asn Pro Tyr Leu Leu Ser His Pro Ser Asp Ser Leu	
400 405 410 415	
gag ctc atg gtc tca gga gca gct gag acc ctc agc cca cca caa aac	1475
Glu Leu Met Val Ser Gly Ala Ala Glu Thr Leu Ser Pro Pro Gln Asn	
420 425 430	
aag tcc gat tcc aag gct gga gca gct aac acc ctc agc cca tca caa	1523
Lys Ser Asp Ser Lys Ala Gly Ala Ala Asn Thr Leu Ser Pro Ser Gln	
435 440 445	
aac aag act gcc tca cac ccc cag gat tac aca gtg gag aat ctc atc	1571
Asn Lys Thr Ala Ser His Pro Gln Asp Tyr Thr Val Glu Asn Leu Ile	
450 455 460	
cgc atg ggc ata gct ggc ttg gtc ctg gtg gtc ctc ggg att ctg cta	1619
Arg Met Gly Ile Ala Gly Leu Val Leu Val Val Leu Gly Ile Leu Leu	
465 470 475	
ttt gag gct cag cac agc cag aga agc ctc tga gatgcagccg ggaggatgaac	1672
Phe Glu Ala Gln His Ser Gln Arg Ser Leu	
480 485	
agcagagaga agaattgacc ctccagagtg gtggagcctt gggaacagat ctgatgatgc	1732
caggagggttc cgggagacaa tttagggctg atgttatctg gactgtctgc caatcatttt	1792
tagagggagg aatcagtggt ggattgcaga gacattttct ggagtgatcc atgaaggacc	1852
attaacatgt gataccttct ctctctatta atgttgactt cccttggttg gatcctct	1910

<210> SEQ ID NO 14

<211> LENGTH: 489

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

Met Thr Pro Ile Val Thr Val Leu Ile Cys Leu Arg Leu Ser Leu Gly	
1 5 10 15	
Pro Arg Thr His Val Gln Ala Gly Thr Leu Pro Lys Pro Thr Leu Trp	
20 25 30	
Ala Glu Pro Gly Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu Trp	
35 40 45	
Cys Gln Gly Ile Leu Glu Thr Gln Glu Tyr Arg Leu Tyr Arg Glu Lys	
50 55 60	
Lys Thr Ala Pro Trp Ile Thr Arg Ile Pro Gln Glu Ile Val Lys Lys	
65 70 75 80	

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Gly Gln Phe Pro Ile Pro Ser Ile Thr Trp Glu His Thr Gly Arg Tyr
 85 90 95

Arg Cys Phe Tyr Gly Ser His Thr Ala Gly Trp Ser Glu Pro Ser Asp
 100 105 110

Pro Leu Glu Leu Val Val Thr Gly Ala Tyr Ile Lys Pro Thr Leu Ser
 115 120 125

Ala Leu Pro Ser Pro Val Val Thr Ser Gly Gly Asn Val Thr Leu His
 130 135 140

Cys Val Ser Gln Val Ala Phe Gly Ser Phe Ile Leu Cys Lys Glu Gly
 145 150 155 160

Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro Arg Thr His Gly
 165 170 175

Trp Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Ser Arg Arg
 180 185 190

Trp Ser Tyr Arg Cys Tyr Ala Tyr Asp Ser Asn Ser Pro His Val Trp
 195 200 205

Ser Leu Pro Ser Asp Leu Leu Glu Leu Leu Val Leu Gly Val Ser Lys
 210 215 220

Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Ile Val Ala Pro Gly Glu
 225 230 235 240

Ser Leu Thr Leu Gln Cys Val Ser Asp Val Ser Tyr Asp Arg Phe Val
 245 250 255

Leu Tyr Lys Glu Gly Glu Arg Asp Phe Leu Gln Leu Pro Gly Pro Gln
 260 265 270

Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser
 275 280 285

Arg Ser Tyr Gly Gly Gln Tyr Arg Cys Ser Gly Ala Tyr Asn Leu Ser
 290 295 300

Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Ala Gly
 305 310 315 320

Gln Phe Arg Gly Arg Pro Phe Ile Ser Val His Pro Gly Pro Thr Val
 325 330 335

Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Trp Gly Pro Phe
 340 345 350

His Thr Phe Leu Leu Thr Lys Ala Gly Ala Ala Asp Ala Pro Leu Arg
 355 360 365

Leu Arg Ser Ile His Glu Tyr Pro Lys Tyr Gln Ala Glu Phe Pro Met
 370 375 380

Ser Pro Val Thr Ser Ala His Ser Gly Thr Tyr Arg Cys Tyr Gly Ser
 385 390 395 400

Leu Ser Ser Asn Pro Tyr Leu Leu Ser His Pro Ser Asp Ser Leu Glu
 405 410 415

Leu Met Val Ser Gly Ala Ala Glu Thr Leu Ser Pro Pro Gln Asn Lys
 420 425 430

Ser Asp Ser Lys Ala Gly Ala Ala Asn Thr Leu Ser Pro Ser Gln Asn
 435 440 445

Lys Thr Ala Ser His Pro Gln Asp Tyr Thr Val Glu Asn Leu Ile Arg
 450 455 460

Met Gly Ile Ala Gly Leu Val Leu Val Val Leu Gly Ile Leu Leu Phe
 465 470 475 480

Glu Ala Gln His Ser Gln Arg Ser Leu
 485

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<210> SEQ ID NO 15
<211> LENGTH: 1725
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (40)..(1491)

<400> SEQUENCE: 15

ctcatccatc cgcagagcag ggcagtgagg ggagacgcc atg acc ccc atc ctc      54
                                     Met Thr Pro Ile Leu
                                     1           5

acg gtc ctg atc tgt ctc ggg ctg agt ctg ggc ccc agg acc cac gtg      102
Thr Val Leu Ile Cys Leu Gly Leu Ser Leu Gly Pro Arg Thr His Val
10           15           20

cag gca ggg cac ctc ccc aag ccc acc ctc tgg gct gag cca ggc tct      150
Gln Ala Gly His Leu Pro Lys Pro Thr Leu Trp Ala Glu Pro Gly Ser
25           30           35

gtg atc atc cag gga agt cct gtg acc ctc agg tgt cag ggg agc ctt      198
Val Ile Ile Gln Gly Ser Pro Val Thr Leu Arg Cys Gln Gly Ser Leu
40           45           50

cag gct gag gag tac cat cta tat agg gaa aac aaa tca gca tcc tgg      246
Gln Ala Glu Glu Tyr His Leu Tyr Arg Glu Asn Lys Ser Ala Ser Trp
55           60           65

gtt aga cgg ata caa gag cct ggg aag aat ggc cag ttc ccc atc cca      294
Val Arg Arg Ile Gln Glu Pro Gly Lys Asn Gly Gln Phe Pro Ile Pro
70           75           80           85

tcc atc acc tgg gaa cac gca ggg cgg tat cac tgt cag tac tac agc      342
Ser Ile Thr Trp Glu His Ala Gly Arg Tyr His Cys Gln Tyr Tyr Ser
90           95           100

cac aat cac tca tca gag tac agt gac ccc ctg gag ctg gtg gtg aca      390
His Asn His Ser Ser Glu Tyr Ser Asp Pro Leu Glu Leu Val Val Thr
105           110           115

gga gcc tac agc aaa ccc acc ctc tca gct ctg ccc agc cct gtg gtg      438
Gly Ala Tyr Ser Lys Pro Thr Leu Ser Ala Leu Pro Ser Pro Val Val
120           125           130

acc tta gga ggg aac gtg acc ctc cag tgt gtc tca cag gtg gca ttt      486
Thr Leu Gly Gly Asn Val Thr Leu Gln Cys Val Ser Gln Val Ala Phe
135           140           145

gac ggc ttc att ctg tgt aag gaa gga gaa gat gaa cac cca caa cgc      534
Asp Gly Phe Ile Leu Cys Lys Glu Gly Glu Asp Glu His Pro Gln Arg
150           155           160           165

ctg aac tcc cat tcc cat gcc cgt ggg tgg tcc tgg gcc atc ttc tcc      582
Leu Asn Ser His Ser His Ala Arg Gly Trp Ser Trp Ala Ile Phe Ser
170           175           180

gtg ggc ccc gtg agc ccg agt cgc agg tgg tcc tac agg tgc tat gct      630
Val Gly Pro Val Ser Pro Ser Arg Arg Trp Ser Tyr Arg Cys Tyr Ala
185           190           195

tat gac tcg aac tct ccc tat gtg tgg tct cta ccc agt gat ctc ctg      678
Tyr Asp Ser Asn Ser Pro Tyr Val Trp Ser Leu Pro Ser Asp Leu Leu
200           205           210

gag ctc ctg gtc cca ggt gtt tct aag aag cca tca ctc tca gtg cag      726
Glu Leu Leu Val Pro Gly Val Ser Lys Lys Pro Ser Leu Ser Val Gln
215           220           225

cca ggt cct atg gtg gcc ccc ggg gag agc ctg acc ctc cag tgt gtc      774
Pro Gly Pro Met Val Ala Pro Gly Glu Ser Leu Thr Leu Gln Cys Val
230           235           240           245

tct gat gtc ggc tac gac aga ttt gtt ctg tat aag gag gga gaa cgt      822
Ser Asp Val Gly Tyr Asp Arg Phe Val Leu Tyr Lys Glu Gly Glu Arg
250           255           260

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gac ttc ctc cag cgc cct ggt tgg cag ccc cag gct ggg ctc tcc cag Asp Phe Leu Gln Arg Pro Gly Trp Gln Pro Gln Ala Gly Leu Ser Gln 265 270 275	870
gcc aac ttc acc ctg ggc cct gtg agc ccc tcc cac ggg ggc cag tac Ala Asn Phe Thr Leu Gly Pro Val Ser Pro Ser His Gly Gly Gln Tyr 280 285 290	918
aga tgc tac agt gca cac aac ctc tcc tcc gag tgg tgg gcc ccc agt Arg Cys Tyr Ser Ala His Asn Leu Ser Ser Glu Trp Ser Ala Pro Ser 295 300 305	966
gac ccc ctg gac atc ctg atc aca gga cag ttc tat gac aga ccc tct Asp Pro Leu Asp Ile Leu Ile Thr Gly Gln Phe Tyr Asp Arg Pro Ser 310 315 320 325	1014
ctc tgg gtg cag cgg gtc ccc aca gta gcc cca gga aag aac gtg acc Leu Ser Val Gln Pro Val Pro Thr Val Ala Pro Gly Lys Asn Val Thr 330 335 340	1062
ctg ctg tgt cag tca cgg ggg cag ttc cac act ttc ctt ctg acc aag Leu Leu Cys Gln Ser Arg Gly Gln Phe His Thr Phe Leu Leu Thr Lys 345 350 355	1110
gag ggg gca ggc cat ccc cca ctg cat ctg aga tca gag cac caa gct Glu Gly Ala Gly His Pro Pro Leu His Leu Arg Ser Glu His Gln Ala 360 365 370	1158
cag cag aac cag gct gaa ttc cgc atg ggt cct gtg acc tca gcc cac Gln Gln Asn Gln Ala Glu Phe Arg Met Gly Pro Val Thr Ser Ala His 375 380 385	1206
gtg ggg acc tac aga tgc tac agc tca ctc agc tcc aac ccc tac ctg Val Gly Thr Tyr Arg Cys Tyr Ser Ser Leu Ser Ser Asn Pro Tyr Leu 390 395 400 405	1254
ctg tct ctc ccc agt gac ccc ctg gag ctc gtg gtc tca gaa gca gct Leu Ser Leu Pro Ser Asp Pro Leu Glu Leu Val Val Ser Glu Ala Ala 410 415 420	1302
gag acc ctc agc cca tca caa aac aag aca gac tcc acg act aca tcc Glu Thr Leu Ser Pro Ser Gln Asn Lys Thr Asp Ser Thr Thr Thr Ser 425 430 435	1350
cta ggc caa cac ccc cag gat tac aca gtg gag aat ctc atc cgc atg Leu Gly Gln His Pro Gln Asp Tyr Thr Val Glu Asn Leu Ile Arg Met 440 445 450	1398
ggt gtg gct ggc ttg gtc ctg gtg gtc ctc ggg att ctg cta ttt gag Gly Val Ala Gly Leu Val Leu Val Val Leu Gly Ile Leu Leu Phe Glu 455 460 465	1446
gct cag cac agc cag aga agc cta caa gat gca gcc ggg agg tga Ala Gln His Ser Gln Arg Ser Leu Gln Asp Ala Ala Gly Arg 470 475 480	1491
acagcagaga ggacaatgca tccttcagcg tgggtggagcc tcagggacag atctgatgat	1551
cccaggaggc tctggaggac aatctaggac ctacattatc tggactgtat gctggtcatt	1611
tctagagaca gcaatcaata tttgagtgtg aggaaactgt ctggggtgat tcctagaaga	1671
tcattaaact gtggtacatt tttttgtcta aaaagcaggt cgtctcgttc caag	1725

<210> SEQ ID NO 16

<211> LENGTH: 483

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Met Thr Pro Ile Leu Thr Val Leu Ile Cys Leu Gly Leu Ser Leu Gly
1 5 10 15

Pro Arg Thr His Val Gln Ala Gly His Leu Pro Lys Pro Thr Leu Trp
20 25 30

Ala Glu Pro Gly Ser Val Ile Ile Gln Gly Ser Pro Val Thr Leu Arg

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35					40					45					
Cys	Gln	Gly	Ser	Leu	Gln	Ala	Glu	Glu	Tyr	His	Leu	Tyr	Arg	Glu	Asn
	50					55					60				
Lys	Ser	Ala	Ser	Trp	Val	Arg	Arg	Ile	Gln	Glu	Pro	Gly	Lys	Asn	Gly
65					70					75				80	
Gln	Phe	Pro	Ile	Pro	Ser	Ile	Thr	Trp	Glu	His	Ala	Gly	Arg	Tyr	His
				85					90					95	
Cys	Gln	Tyr	Tyr	Ser	His	Asn	His	Ser	Ser	Glu	Tyr	Ser	Asp	Pro	Leu
			100					105					110		
Glu	Leu	Val	Val	Thr	Gly	Ala	Tyr	Ser	Lys	Pro	Thr	Leu	Ser	Ala	Leu
		115					120					125			
Pro	Ser	Pro	Val	Val	Thr	Leu	Gly	Gly	Asn	Val	Thr	Leu	Gln	Cys	Val
		130				135					140				
Ser	Gln	Val	Ala	Phe	Asp	Gly	Phe	Ile	Leu	Cys	Lys	Glu	Gly	Glu	Asp
145					150					155					160
Glu	His	Pro	Gln	Arg	Leu	Asn	Ser	His	Ser	His	Ala	Arg	Gly	Trp	Ser
				165					170					175	
Trp	Ala	Ile	Phe	Ser	Val	Gly	Pro	Val	Ser	Pro	Ser	Arg	Arg	Trp	Ser
			180					185					190		
Tyr	Arg	Cys	Tyr	Ala	Tyr	Asp	Ser	Asn	Ser	Pro	Tyr	Val	Trp	Ser	Leu
		195					200					205			
Pro	Ser	Asp	Leu	Leu	Glu	Leu	Leu	Val	Pro	Gly	Val	Ser	Lys	Lys	Pro
		210				215					220				
Ser	Leu	Ser	Val	Gln	Pro	Gly	Pro	Met	Val	Ala	Pro	Gly	Glu	Ser	Leu
225					230					235					240
Thr	Leu	Gln	Cys	Val	Ser	Asp	Val	Gly	Tyr	Asp	Arg	Phe	Val	Leu	Tyr
				245					250					255	
Lys	Glu	Gly	Glu	Arg	Asp	Phe	Leu	Gln	Arg	Pro	Gly	Trp	Gln	Pro	Gln
			260					265					270		
Ala	Gly	Leu	Ser	Gln	Ala	Asn	Phe	Thr	Leu	Gly	Pro	Val	Ser	Pro	Ser
		275					280					285			
His	Gly	Gly	Gln	Tyr	Arg	Cys	Tyr	Ser	Ala	His	Asn	Leu	Ser	Ser	Glu
	290					295					300				
Trp	Ser	Ala	Pro	Ser	Asp	Pro	Leu	Asp	Ile	Leu	Ile	Thr	Gly	Gln	Phe
305					310					315					320
Tyr	Asp	Arg	Pro	Ser	Leu	Ser	Val	Gln	Pro	Val	Pro	Thr	Val	Ala	Pro
				325					330					335	
Gly	Lys	Asn	Val	Thr	Leu	Leu	Cys	Gln	Ser	Arg	Gly	Gln	Phe	His	Thr
			340					345					350		
Phe	Leu	Leu	Thr	Lys	Glu	Gly	Ala	Gly	His	Pro	Pro	Leu	His	Leu	Arg
		355					360					365			
Ser	Glu	His	Gln	Ala	Gln	Gln	Asn	Gln	Ala	Glu	Phe	Arg	Met	Gly	Pro
	370					375					380				
Val	Thr	Ser	Ala	His	Val	Gly	Thr	Tyr	Arg	Cys	Tyr	Ser	Ser	Leu	Ser
385					390					395					400
Ser	Asn	Pro	Tyr	Leu	Leu	Ser	Leu	Pro	Ser	Asp	Pro	Leu	Glu	Leu	Val
				405					410					415	
Val	Ser	Glu	Ala	Ala	Glu	Thr	Leu	Ser	Pro	Ser	Gln	Asn	Lys	Thr	Asp
			420					425					430		
Ser	Thr	Thr	Thr	Ser	Leu	Gly	Gln	His	Pro	Gln	Asp	Tyr	Thr	Val	Glu
		435					440					445			
Asn	Leu	Ile	Arg	Met	Gly	Val	Ala	Gly	Leu	Val	Leu	Val	Val	Leu	Gly
	450					455					460				

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Ile Leu Leu Phe Glu Ala Gln His Ser Gln Arg Ser Leu Gln Asp Ala
465                470                475                480

Ala Gly Arg

<210> SEQ ID NO 17
<211> LENGTH: 1625
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (30)..(1376)

<400> SEQUENCE: 17

cacagctggg gcccttggga ggagacgcc atg atc ccc acc ttc acg gct ctg      53
                               Met Ile Pro Thr Phe Thr Ala Leu
                               1                    5

ctc tgc ctc ggg ctg agt ctg ggc ccc agg acc cac atg cag gca ggg      101
Leu Cys Leu Gly Leu Ser Leu Gly Pro Arg Thr His Met Gln Ala Gly
 10                    15                    20

ccc ctc ccc aaa ccc acc ctc tgg gct gag cca ggc tct gtg atc agc      149
Pro Leu Pro Lys Pro Thr Leu Trp Ala Glu Pro Gly Ser Val Ile Ser
25                    30                    35                    40

tgg ggg aac tct gtg acc atc tgg tgt cag ggg acc ctg gag gct cgg      197
Trp Gly Asn Ser Val Thr Ile Trp Cys Gln Gly Thr Leu Glu Ala Arg
 45                    50                    55

gag tac cgt ctg gat aaa gag gaa agc cca gca ccc tgg gac aga cag      245
Glu Tyr Arg Leu Asp Lys Glu Glu Ser Pro Ala Pro Trp Asp Arg Gln
 60                    65                    70

aac cca ctg gag ccc aag aac aag gcc aga ttc tcc atc cca tcc atg      293
Asn Pro Leu Glu Pro Lys Asn Lys Ala Arg Phe Ser Ile Pro Ser Met
 75                    80                    85

aca gag gac tat gca ggg aga tac cgc tgt tac tat cgc agc cct gta      341
Thr Glu Asp Tyr Ala Gly Arg Tyr Arg Cys Tyr Tyr Arg Ser Pro Val
 90                    95                    100

ggc tgg tca cag ccc agt gac ccc ctg gag ctg gtg atg aca gga gcc      389
Gly Trp Ser Gln Pro Ser Asp Pro Leu Glu Leu Val Met Thr Gly Ala
105                    110                    115                    120

tac agt aaa ccc acc ctt tca gcc ctg ccg agt cct ctt gtg acc tca      437
Tyr Ser Lys Pro Thr Leu Ser Ala Leu Pro Ser Pro Leu Val Thr Ser
125                    130                    135

gga aag agc gtg acc ctg ctg tgt cag tca cgg agc cca atg gac act      485
Gly Lys Ser Val Thr Leu Leu Cys Gln Ser Arg Ser Pro Met Asp Thr
140                    145                    150

ttt ctt ctg atc aag gag cgg gca gcc cat ccc cta ctg cat ctg aga      533
Phe Leu Leu Ile Lys Glu Arg Ala Ala His Pro Leu Leu His Leu Arg
155                    160                    165

tca gag cac gga gct cag cag cac cag gct gaa ttc ccc atg agt cct      581
Ser Glu His Gly Ala Gln Gln His Gln Ala Glu Phe Pro Met Ser Pro
170                    175                    180

gtg acc tca gtg cac ggg ggg acc tac agg tgc ttc agc tca cac ggc      629
Val Thr Ser Val His Gly Gly Thr Tyr Arg Cys Phe Ser Ser His Gly
185                    190                    195                    200

ttc tcc cac tac ctg ctg tca cac ccc agt gac ccc ctg gag ctc ata      677
Phe Ser His Tyr Leu Leu Ser His Pro Ser Asp Pro Leu Glu Leu Ile
205                    210                    215

gtc tca gga tcc ttg gag ggt ccc agg ccc tca ccc aca agg tcc gtc      725
Val Ser Gly Ser Leu Glu Gly Pro Arg Pro Ser Pro Thr Arg Ser Val
220                    225                    230

tca aca gct gca ggc cct gag gac cag ccc ctc atg cct aca ggg tca      773
Ser Thr Ala Ala Gly Pro Glu Asp Gln Pro Leu Met Pro Thr Gly Ser

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235	240	245	
gtc ccc cac agt ggt ctg aga agg cac tgg gag gta ctg atc ggg gtc Val Pro His Ser Gly Leu Arg Arg His Trp Glu Val Leu Ile Gly Val			821
250	255	260	
ttg gtg gtc tcc atc ctg ctt ctc tcc ctc ctc ttc ctc ctc ctc			869
Leu Val Val Ser Ile Leu Leu Leu Ser Leu Leu Leu Phe Leu Leu Leu	270	275	280
265			
caa cac tgg cgt cag gga aaa cac agg aca ttg gcc cag aga cag gct			917
Gln His Trp Arg Gln Gly Lys His Arg Thr Leu Ala Gln Arg Gln Ala	285	290	295
gat ttc caa cgt cct cca ggg gct gcc gag cca gag ccc aag gac ggg			965
Asp Phe Gln Arg Pro Pro Gly Ala Ala Glu Pro Glu Pro Lys Asp Gly	300	305	310
ggc cta cag agg agg tcc agc cca gct gct gac gtc cag gga gaa aac			1013
Gly Leu Gln Arg Arg Ser Ser Pro Ala Ala Asp Val Gln Gly Glu Asn	315	320	325
ttc tgt gct gcc gtg aag aac aca cag cct gag gac ggg gtg gaa atg			1061
Phe Cys Ala Ala Val Lys Asn Thr Gln Pro Glu Asp Gly Val Glu Met	330	335	340
gac act cgg cag agc cca cac gat gaa gac ccc cag gca gtg acg tat			1109
Asp Thr Arg Gln Ser Pro His Asp Glu Asp Pro Gln Ala Val Thr Tyr	345	350	355
gcc aag gtg aaa cac tcc aga cct agg aga gaa atg gcc tct cct ccc			1157
Ala Lys Val Lys His Ser Arg Pro Arg Arg Glu Met Ala Ser Pro Pro	365	370	375
tcc cca ctg tct ggg gaa ttc ctg gac aca aag gac aga cag gca gaa			1205
Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu	380	385	390
gag gac aga cag atg gac act gag gct gct gca tct gaa gcc ccc cag			1253
Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Pro Gln	395	400	405
gat gtg acc tac gcc cgg ctg cac agc ttt acc ctc aga cag aag gca			1301
Asp Val Thr Tyr Ala Arg Leu His Ser Phe Thr Leu Arg Gln Lys Ala	410	415	420
act gag cct cct cca tcc cag gaa ggg gcc tct cca gct gag ccc agt			1349
Thr Glu Pro Pro Pro Ser Gln Glu Gly Ala Ser Pro Ala Glu Pro Ser	425	430	435
			440
gtc tat gcc act ctg gcc atc cac taa tccagggggg acccagacc			1396
Val Tyr Ala Thr Leu Ala Ile His	445		
cacaagccat ggagactcag gaccccgaa ggcatggaag ctgcctccag tagacatcac			1456
tgaaccccag ccagcccaga cccctgacac agaccactag aagattccgg gaacgttggg			1516
agtcacctga ttctgcgaaag ataaataata tccctgcatt atcaaaataa agtagcagac			1576
ctctcaattc acaatgagtt aactgataaa acaaaacaga agtcaaaaa			1625

<210> SEQ ID NO 18

<211> LENGTH: 448

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Met Ile Pro Thr Phe Thr Ala Leu Leu Cys Leu Gly Leu Ser Leu Gly
1 5 10 15Pro Arg Thr His Met Gln Ala Gly Pro Leu Pro Lys Pro Thr Leu Trp
20 25 30Ala Glu Pro Gly Ser Val Ile Ser Trp Gly Asn Ser Val Thr Ile Trp
35 40 45

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Cys Gln Gly Thr Leu Glu Ala Arg Glu Tyr Arg Leu Asp Lys Glu Glu
 50 55 60
 Ser Pro Ala Pro Trp Asp Arg Gln Asn Pro Leu Glu Pro Lys Asn Lys
 65 70 75 80
 Ala Arg Phe Ser Ile Pro Ser Met Thr Glu Asp Tyr Ala Gly Arg Tyr
 85 90 95
 Arg Cys Tyr Tyr Arg Ser Pro Val Gly Trp Ser Gln Pro Ser Asp Pro
 100 105 110
 Leu Glu Leu Val Met Thr Gly Ala Tyr Ser Lys Pro Thr Leu Ser Ala
 115 120 125
 Leu Pro Ser Pro Leu Val Thr Ser Gly Lys Ser Val Thr Leu Leu Cys
 130 135 140
 Gln Ser Arg Ser Pro Met Asp Thr Phe Leu Leu Ile Lys Glu Arg Ala
 145 150 155 160
 Ala His Pro Leu Leu His Leu Arg Ser Glu His Gly Ala Gln Gln His
 165 170 175
 Gln Ala Glu Phe Pro Met Ser Pro Val Thr Ser Val His Gly Gly Thr
 180 185 190
 Tyr Arg Cys Phe Ser Ser His Gly Phe Ser His Tyr Leu Leu Ser His
 195 200 205
 Pro Ser Asp Pro Leu Glu Leu Ile Val Ser Gly Ser Leu Glu Gly Pro
 210 215 220
 Arg Pro Ser Pro Thr Arg Ser Val Ser Thr Ala Ala Gly Pro Glu Asp
 225 230 235 240
 Gln Pro Leu Met Pro Thr Gly Ser Val Pro His Ser Gly Leu Arg Arg
 245 250 255
 His Trp Glu Val Leu Ile Gly Val Leu Val Val Ser Ile Leu Leu Leu
 260 265 270
 Ser Leu Leu Leu Phe Leu Leu Leu Gln His Trp Arg Gln Gly Lys His
 275 280 285
 Arg Thr Leu Ala Gln Arg Gln Ala Asp Phe Gln Arg Pro Pro Gly Ala
 290 295 300
 Ala Glu Pro Glu Pro Lys Asp Gly Gly Leu Gln Arg Arg Ser Ser Pro
 305 310 315 320
 Ala Ala Asp Val Gln Gly Glu Asn Phe Cys Ala Ala Val Lys Asn Thr
 325 330 335
 Gln Pro Glu Asp Gly Val Glu Met Asp Thr Arg Gln Ser Pro His Asp
 340 345 350
 Glu Asp Pro Gln Ala Val Thr Tyr Ala Lys Val Lys His Ser Arg Pro
 355 360 365
 Arg Arg Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu
 370 375 380
 Asp Thr Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu
 385 390 395 400
 Ala Ala Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Arg Leu His
 405 410 415
 Ser Phe Thr Leu Arg Gln Lys Ala Thr Glu Pro Pro Pro Ser Gln Glu
 420 425 430
 Gly Ala Ser Pro Ala Glu Pro Ser Val Tyr Ala Thr Leu Ala Ile His
 435 440 445

<210> SEQ ID NO 19

<211> LENGTH: 2194

<212> TYPE: DNA

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<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (67)..(1962)

<400> SEQUENCE: 19

tctctgtcct gccagcactg agggctcacc cctctgcaga gcgcgggggc accggaagga      60

gacgcc atg acg ccc gcc ctc aca gcc ctg ctc tgc ctt ggg ctg agt      108
Met Thr Pro Ala Leu Thr Ala Leu Leu Cys Leu Gly Leu Ser
      1          5          10

ctg ggc ccc agg acc cgc gtg cag gca ggg ccc ttc ccc aaa ccc acc      156
Leu Gly Pro Arg Thr Arg Val Gln Ala Gly Pro Phe Pro Lys Pro Thr
15          20          25          30

ctc tgg gct gag cca ggc tct gtg atc agc tgg ggg agc ccc gtg acc      204
Leu Trp Ala Glu Pro Gly Ser Val Ile Ser Trp Gly Ser Pro Val Thr
          35          40          45

atc tgg tgt cag ggg agc ctg gag gcc cag gag tac caa ctg gat aaa      252
Ile Trp Cys Gln Gly Ser Leu Glu Ala Gln Glu Tyr Gln Leu Asp Lys
50          55          60

gag gga agc cca gag ccc ttg gac aga aat aac cca ctg gaa ccc aag      300
Glu Gly Ser Pro Glu Pro Leu Asp Arg Asn Asn Pro Leu Glu Pro Lys
65          70          75

aac aag gcc aga ttc tcc atc cca tcc atg aca cag cac cat gca ggg      348
Asn Lys Ala Arg Phe Ser Ile Pro Ser Met Thr Gln His His Ala Gly
80          85          90

aga tac cgc tgc cac tat tac agc tct gca ggc tgg tca gag ccc agc      396
Arg Tyr Arg Cys His Tyr Tyr Ser Ser Ala Gly Trp Ser Glu Pro Ser
95          100          105          110

gac ccc ctg gag ctg gtg atg aca gga gcc tat agc aaa ccc acc ctc      444
Asp Pro Leu Glu Leu Val Met Thr Gly Ala Tyr Ser Lys Pro Thr Leu
115          120          125

tca gcc ctg ccc agc cct gtg gtg gcc tca ggg ggg aat atg acc ctc      492
Ser Ala Leu Pro Ser Pro Val Val Ala Ser Gly Gly Asn Met Thr Leu
130          135          140

cga tgt ggc tca cag aag aga tat cac cat ttt gtt ctg atg aag gaa      540
Arg Cys Gly Ser Gln Lys Arg Tyr His His Phe Val Leu Met Lys Glu
145          150          155

gga gaa cac cag ctc ccc cgg acc ctg gac tca cag cag ctc cac agt      588
Gly Glu His Gln Leu Pro Arg Thr Leu Asp Ser Gln Gln Leu His Ser
160          165          170

ggg ggg ttc cag gcc ctg ttc cct gtg ggc ccc gtg aac ccc agc cac      636
Gly Gly Phe Gln Ala Leu Phe Pro Val Gly Pro Val Asn Pro Ser His
175          180          185          190

agg tgg agg ttc aca tgc tat tac tat atg aac acc ccc cgg gtg      684
Arg Trp Arg Phe Thr Cys Tyr Tyr Tyr Tyr Met Asn Thr Pro Arg Val
195          200          205

tgg tcc cac ccc agt gac ccc ctg gag att ctg ccc tca ggc gtg tct      732
Trp Ser His Pro Ser Asp Pro Leu Glu Ile Leu Pro Ser Gly Val Ser
210          215          220

agg aag ccc tcc ctc ctg acc ctg cag ggc cct gtc ctg gcc cct ggg      780
Arg Lys Pro Ser Leu Leu Thr Leu Gln Gly Pro Val Leu Ala Pro Gly
225          230          235

cag agt ctg acc ctc cag tgt ggc tct gat gtc ggc tac gac aga ttt      828
Gln Ser Leu Thr Leu Gln Cys Gly Ser Asp Val Gly Tyr Asp Arg Phe
240          245          250

gtt ctg tat aag gag ggg gaa cgt gac ttc ctc cag cgc cct ggc cag      876
Val Leu Tyr Lys Glu Gly Glu Arg Asp Phe Leu Gln Arg Pro Gly Gln
255          260          265          270

cag ccc cag gct ggg ctc tcc cag gcc aac ttc acc ctg ggc cct gtg      924
Gln Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val

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275										280					285					
agc	ccc	tcc	aat	ggg	ggc	cag	tac	agg	tgc	tac	ggt	gca	cac	aac	ctc		972			
Ser	Pro	Ser	Asn	Gly	Gly	Gln	Tyr	Arg	Cys	Tyr	Gly	Ala	His	Asn	Leu					
			290					295					300							
tcc	tcc	gag	tgg	tcg	gcc	ccc	agc	gac	ccc	ctg	aac	atc	ctg	atg	gca		1020			
Ser	Ser	Glu	Trp	Ser	Ala	Pro	Ser	Asp	Pro	Leu	Asn	Ile	Leu	Met	Ala					
		305					310					315								
gga	cag	atc	tat	gac	acc	gtc	tcc	ctg	tca	gca	cag	ccg	ggc	ccc	aca		1068			
Gly	Gln	Ile	Tyr	Asp	Thr	Val	Ser	Leu	Ser	Ala	Gln	Pro	Gly	Pro	Thr					
	320					325					330									
gtg	gcc	tca	gga	gag	aac	gtg	acc	ctg	ctg	tgt	cag	tca	tgg	tgg	cag		1116			
Val	Ala	Ser	Gly	Glu	Asn	Val	Thr	Leu	Leu	Cys	Gln	Ser	Trp	Trp	Gln					
	335				340					345					350					
ttt	gac	act	ttc	ctt	ctg	acc	aaa	gaa	ggg	gca	gcc	cat	ccc	cca	ctg		1164			
Phe	Asp	Thr	Phe	Leu	Leu	Thr	Lys	Glu	Gly	Ala	Ala	His	Pro	Pro	Leu					
				355				360						365						
cgt	ctg	aga	tca	atg	tac	gga	gct	cat	aag	tac	cag	gct	gaa	ttc	ccc		1212			
Arg	Leu	Arg	Ser	Met	Tyr	Gly	Ala	His	Lys	Tyr	Gln	Ala	Glu	Phe	Pro					
			370					375						380						
atg	agt	cct	gtg	acc	tca	gcc	cac	gcg	ggg	acc	tac	agg	tgc	tac	ggc		1260			
Met	Ser	Pro	Val	Thr	Ser	Ala	His	Ala	Gly	Thr	Tyr	Arg	Cys	Tyr	Gly					
		385					390						395							
tca	cgc	agc	tcc	aac	ccc	tac	ctg	ctg	tct	cac	ccc	agt	gag	ccc	ctg		1308			
Ser	Arg	Ser	Ser	Asn	Pro	Tyr	Leu	Leu	Ser	His	Pro	Ser	Glu	Pro	Leu					
	400					405					410									
gag	ctc	gtg	gtc	tca	gga	cac	tct	gga	ggc	tcc	agc	ctc	cca	ccc	aca		1356			
Glu	Leu	Val	Val	Ser	Gly	His	Ser	Gly	Gly	Ser	Ser	Leu	Pro	Pro	Thr					
	415				420					425					430					
ggg	ccg	ccc	tcc	aca	cct	ggt	ctg	gga	aga	tac	ctg	gag	ggt	ttg	att		1404			
Gly	Pro	Pro	Ser	Thr	Pro	Gly	Leu	Gly	Arg	Tyr	Leu	Glu	Val	Leu	Ile					
				435					440					445						
ggg	gtc	tcg	gtg	gcc	ttc	gtc	ctg	ctg	ctc	ttc	ctc	ctc	ctc	ttc	ctc		1452			
Gly	Val	Ser	Val	Ala	Phe	Val	Leu	Leu	Phe	Leu	Leu	Leu	Leu	Phe	Leu					
			450					455						460						
ctc	ctc	cga	cgt	cag	cgt	cac	agc	aaa	cac	agg	aca	tct	gac	cag	aga		1500			
Leu	Leu	Arg	Arg	Gln	Arg	His	Ser	Lys	His	Arg	Thr	Ser	Asp	Gln	Arg					
		465				470							475							
aag	act	gat	ttc	cag	cgt	cct	gca	ggg	gct	gcg	gag	aca	gag	ccc	aag		1548			
Lys	Thr	Asp	Phe	Gln	Arg	Pro	Ala	Gly	Ala	Ala	Glu	Thr	Glu	Pro	Lys					
		480				485							490							
gac	agg	ggc	ctg	ctg	agg	agg	tcc	agc	cca	gct	gct	gac	gtc	cag	gaa		1596			
Asp	Arg	Gly	Leu	Leu	Arg	Arg	Ser	Ser	Pro	Ala	Ala	Asp	Val	Gln	Glu					
	495				500					505					510					
gaa	aac	ctc	tat	gct	gcc	gtg	aag	gac	aca	cag	tct	gag	gac	ggg	gtg		1644			
Glu	Asn	Leu	Tyr	Ala	Ala	Val	Lys	Asp	Thr	Gln	Ser	Glu	Asp	Gly	Val					
				515					520					525						
gag	ctg	gac	agt	cag	agc	cca	cac	gat	gaa	gac	ccc	cac	gca	gtg	acg		1692			
Glu	Leu	Asp	Ser	Gln	Ser	Pro	His	Asp	Glu	Asp	Pro	His	Ala	Val	Thr					
			530					535					540							
tat	gcc	ccg	gtg	aaa	cac	tcc	agt	cct	agg	aga	gaa	atg	gcc	tct	cct		1740			
Tyr	Ala	Pro	Val	Lys	His	Ser	Ser	Pro	Arg	Arg	Glu	Met	Ala	Ser	Pro					
			545				550						555							
cct	tcc	cca	ctg	tct	ggg	gaa	ttc	ctg	gac	aca	aag	gac	aga	cag	gca		1788			
Pro	Ser	Pro	Leu	Ser	Gly	Glu	Phe	Leu	Asp	Thr	Lys	Asp	Arg	Gln	Ala					
		560				565							570							
gaa	gag	gac	aga	cag	atg	gac	act	gag	gct	gct	gca	tct	gaa	gcc	tcc		1836			
Glu	Glu	Asp	Arg	Gln	Met	Asp	Thr	Glu	Ala	Ala	Ala	Ser	Glu	Ala	Ser					
		575			580					585					590					
cag	gat	gtg	acc	tac	gcc	cag	ctg	cac	agc	ttg	acc	ctt	aga	cgg	aag		1884			

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Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg Lys
595 600 605

gca act gag cct cct cca tcc cag gaa ggg gaa cct cca gct gag ccc 1932
Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Glu Pro Pro Ala Glu Pro
610 615 620

agc atc tac gcc act ctg gcc atc cac tag cccggggggg acgcagaccc 1982
Ser Ile Tyr Ala Thr Leu Ala Ile His
625 630

cacactcagc agaaggagac tcaggactgc tgaaggacgg gagctgcccc cagtggacac 2042

cagtgaaccc cagtcagcct ggaccctaa cacagacat gaggagacgc tgggaacttg 2102

tgggactcac ctgactcaaa gatgactaat atcgtcccat tttggaaata aagcaacaga 2162

cttctcaagc aggtcgtctc gttccaagat ct 2194

<210> SEQ ID NO 20

<211> LENGTH: 631

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Met Thr Pro Ala Leu Thr Ala Leu Leu Cys Leu Gly Leu Ser Leu Gly
1 5 10 15

Pro Arg Thr Arg Val Gln Ala Gly Pro Phe Pro Lys Pro Thr Leu Trp
20 25 30

Ala Glu Pro Gly Ser Val Ile Ser Trp Gly Ser Pro Val Thr Ile Trp
35 40 45

Cys Gln Gly Ser Leu Glu Ala Gln Glu Tyr Gln Leu Asp Lys Glu Gly
50 55 60

Ser Pro Glu Pro Leu Asp Arg Asn Asn Pro Leu Glu Pro Lys Asn Lys
65 70 75 80

Ala Arg Phe Ser Ile Pro Ser Met Thr Gln His His Ala Gly Arg Tyr
85 90 95

Arg Cys His Tyr Tyr Ser Ser Ala Gly Trp Ser Glu Pro Ser Asp Pro
100 105 110

Leu Glu Leu Val Met Thr Gly Ala Tyr Ser Lys Pro Thr Leu Ser Ala
115 120 125

Leu Pro Ser Pro Val Val Ala Ser Gly Gly Asn Met Thr Leu Arg Cys
130 135 140

Gly Ser Gln Lys Arg Tyr His His Phe Val Leu Met Lys Glu Gly Glu
145 150 155 160

His Gln Leu Pro Arg Thr Leu Asp Ser Gln Gln Leu His Ser Gly Gly
165 170 175

Phe Gln Ala Leu Phe Pro Val Gly Pro Val Asn Pro Ser His Arg Trp
180 185 190

Arg Phe Thr Cys Tyr Tyr Tyr Tyr Met Asn Thr Pro Arg Val Trp Ser
195 200 205

His Pro Ser Asp Pro Leu Glu Ile Leu Pro Ser Gly Val Ser Arg Lys
210 215 220

Pro Ser Leu Leu Thr Leu Gln Gly Pro Val Leu Ala Pro Gly Gln Ser
225 230 235 240

Leu Thr Leu Gln Cys Gly Ser Asp Val Gly Tyr Asp Arg Phe Val Leu
245 250 255

Tyr Lys Glu Gly Glu Arg Asp Phe Leu Gln Arg Pro Gly Gln Gln Pro
260 265 270

Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser Pro

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275					280					285					
Ser	Asn	Gly	Gly	Gln	Tyr	Arg	Cys	Tyr	Gly	Ala	His	Asn	Leu	Ser	Ser
	290					295					300				
Glu	Trp	Ser	Ala	Pro	Ser	Asp	Pro	Leu	Asn	Ile	Leu	Met	Ala	Gly	Gln
	305					310					315				320
Ile	Tyr	Asp	Thr	Val	Ser	Leu	Ser	Ala	Gln	Pro	Gly	Pro	Thr	Val	Ala
				325					330					335	
Ser	Gly	Glu	Asn	Val	Thr	Leu	Leu	Cys	Gln	Ser	Trp	Trp	Gln	Phe	Asp
			340					345					350		
Thr	Phe	Leu	Leu	Thr	Lys	Glu	Gly	Ala	Ala	His	Pro	Pro	Leu	Arg	Leu
		355					360					365			
Arg	Ser	Met	Tyr	Gly	Ala	His	Lys	Tyr	Gln	Ala	Glu	Phe	Pro	Met	Ser
	370					375					380				
Pro	Val	Thr	Ser	Ala	His	Ala	Gly	Thr	Tyr	Arg	Cys	Tyr	Gly	Ser	Arg
	385					390					395				400
Ser	Ser	Asn	Pro	Tyr	Leu	Leu	Ser	His	Pro	Ser	Glu	Pro	Leu	Glu	Leu
				405					410					415	
Val	Val	Ser	Gly	His	Ser	Gly	Gly	Ser	Ser	Leu	Pro	Pro	Thr	Gly	Pro
			420					425					430		
Pro	Ser	Thr	Pro	Gly	Leu	Gly	Arg	Tyr	Leu	Glu	Val	Leu	Ile	Gly	Val
		435					440					445			
Ser	Val	Ala	Phe	Val	Leu	Leu	Leu	Phe	Leu	Leu	Leu	Phe	Leu	Leu	Leu
	450					455					460				
Arg	Arg	Gln	Arg	His	Ser	Lys	His	Arg	Thr	Ser	Asp	Gln	Arg	Lys	Thr
	465					470					475				480
Asp	Phe	Gln	Arg	Pro	Ala	Gly	Ala	Ala	Glu	Thr	Glu	Pro	Lys	Asp	Arg
				485					490					495	
Gly	Leu	Leu	Arg	Arg	Ser	Ser	Pro	Ala	Ala	Asp	Val	Gln	Glu	Glu	Asn
			500					505					510		
Leu	Tyr	Ala	Ala	Val	Lys	Asp	Thr	Gln	Ser	Glu	Asp	Gly	Val	Glu	Leu
		515					520					525			
Asp	Ser	Gln	Ser	Pro	His	Asp	Glu	Asp	Pro	His	Ala	Val	Thr	Tyr	Ala
	530					535					540				
Pro	Val	Lys	His	Ser	Ser	Pro	Arg	Arg	Glu	Met	Ala	Ser	Pro	Pro	Ser
	545					550					555				560
Pro	Leu	Ser	Gly	Glu	Phe	Leu	Asp	Thr	Lys	Asp	Arg	Gln	Ala	Glu	Glu
				565					570					575	
Asp	Arg	Gln	Met	Asp	Thr	Glu	Ala	Ala	Ala	Ser	Glu	Ala	Ser	Gln	Asp
			580					585						590	
Val	Thr	Tyr	Ala	Gln	Leu	His	Ser	Leu	Thr	Leu	Arg	Arg	Lys	Ala	Thr
		595					600					605			
Glu	Pro	Pro	Pro	Ser	Gln	Glu	Gly	Glu	Pro	Pro	Ala	Glu	Pro	Ser	Ile
	610					615					620				
Tyr	Ala	Thr	Leu	Ala	Ile	His									
	625					630									

<210> SEQ ID NO 21
 <211> LENGTH: 2061
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (67)..(1839)
 <400> SEQUENCE: 21

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Met Thr Leu Thr Leu Ser Val Leu Ile Cys Leu Gly Leu Ser	
1 5 10	
gtg gcc ccc agg acc tgc gtg cag gca gcc acc ctc ccc aaa ccc acc	156
Val Gly Pro Arg Thr Cys Val Gln Ala Gly Thr Leu Pro Lys Pro Thr	
15 20 25 30	
ctc tgg gct gag cca gcc tct gtg ata gct cgg ggg aag ccc gtg acc	204
Leu Trp Ala Glu Pro Ala Ser Val Ile Ala Arg Gly Lys Pro Val Thr	
35 40 45	
ctc tgg tgt cag ggg ccc ctg gag act gag gag tac cgt ctg gat aag	252
Leu Trp Cys Gln Gly Pro Leu Glu Thr Glu Glu Tyr Arg Leu Asp Lys	
50 55 60	
gag gga ctc cca tgg gcc cgg aag aga cag aac cca ctg gag cct gga	300
Glu Gly Leu Pro Trp Ala Arg Lys Arg Gln Asn Pro Leu Glu Pro Gly	
65 70 75	
gcc aag gcc aag ttc cac att cca tcc acg gtg tat gac agt gca ggg	348
Ala Lys Ala Lys Phe His Ile Pro Ser Thr Val Tyr Asp Ser Ala Gly	
80 85 90	
cga tac cgc tgc tac tat gag acc cct gca gcc tgg tca gag ccc agt	396
Arg Tyr Arg Cys Tyr Tyr Glu Thr Pro Ala Gly Trp Ser Glu Pro Ser	
95 100 105 110	
gac ccc ctg gag ctg gtg gcg aca gga ttc tat gca gaa ccc act ctt	444
Asp Pro Leu Glu Leu Val Ala Thr Gly Phe Tyr Ala Glu Pro Thr Leu	
115 120 125	
tta gcc ctg ccg agt cct gtg gtg gcc tca gga gga aat gtg acc ctc	492
Leu Ala Leu Pro Ser Pro Val Val Ala Ser Gly Gly Asn Val Thr Leu	
130 135 140	
cag tgt gat aca ctg gac gga ctt ctc acg ttt gtt ctt gtt gag gaa	540
Gln Cys Asp Thr Leu Asp Gly Leu Leu Thr Phe Val Leu Val Glu Glu	
145 150 155	
gaa cag aag ctc ccc agg acc ctg tac tca cag aag ctc ccc aaa ggg	588
Glu Gln Lys Leu Pro Arg Thr Leu Tyr Ser Gln Lys Leu Pro Lys Gly	
160 165 170	
cca tcc cag gcc ctg ttc cct gtg ggt ccc gtg acc ccc agc tgc agg	636
Pro Ser Gln Ala Leu Phe Pro Val Gly Pro Val Thr Pro Ser Cys Arg	
175 180 185 190	
tgg agg ttc aga tgc tat tac tat tac agg aaa aac cct cag gtg tgg	684
Trp Arg Phe Arg Cys Tyr Tyr Tyr Tyr Arg Lys Asn Pro Gln Val Trp	
195 200 205	
tcg aac ccc agt gac ctc ctg gag att ctg gtc cca gcc gtg tct agg	732
Ser Asn Pro Ser Asp Leu Leu Glu Ile Leu Val Pro Gly Val Ser Arg	
210 215 220	
aag ccc tcc ctc ctg atc ccg cag gcc tct gtc gtg gcc cgc gga gcc	780
Lys Pro Ser Pro Leu Ile Pro Gln Gly Ser Val Val Ala Arg Gly Gly	
225 230 235	
agc ctg acc ctg cag tgt cgc tct gat gtc gcc tat gac ata ttc gtt	828
Ser Leu Thr Leu Gln Cys Arg Ser Asp Val Gly Tyr Asp Ile Phe Val	
240 245 250	
ctg tac aag gag ggg gaa cat gac ctc gtc cag gcc tct gcc cag cag	876
Leu Tyr Lys Glu Gly Glu His Asp Leu Val Gln Gly Ser Gly Gln Gln	
255 260 265 270	
ccc cag gct ggg ctc tcc cag gcc aac ttc acc ctg gcc cct gtg agc	924
Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser	
275 280 285	
cgc tcc cac ggg gcc cag tac aga tgc tac ggt gca cac aac ctc tcc	972
Arg Ser His Gly Gly Gln Tyr Arg Cys Tyr Gly Ala His Asn Leu Ser	
290 295 300	
cct agg tgg tcg gcc ccc agc gac ccc ctg gac atc ctg atc gca gga	1020

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Pro Arg Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Ala Gly 305 310 315	
ctg atc cct gac ata ccc gcc ctc tcg gtg cag ccg ggc ccc aag gtg Leu Ile Pro Asp Ile Pro Ala Leu Ser Val Gln Pro Gly Pro Lys Val 320 325 330	1068
gcc tca gga gag aac gtg acc ctg ctg tgt cag tca tgg cat cag ata Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Trp His Gln Ile 335 340 345 350	1116
gac act ttc ttt ttg acc aag gag ggg gca gcc cat ccc ccg ctg tgt Asp Thr Phe Phe Leu Thr Lys Glu Gly Ala Ala His Pro Pro Leu Cys 355 360 365	1164
cta aag tca aag tac cag tct tat aga cac cag gct gaa ttc tcc atg Leu Lys Ser Lys Tyr Gln Ser Tyr Arg His Gln Ala Glu Phe Ser Met 370 375 380	1212
agt cct gtg acc tca gcc cag ggt gga acc tac cga tgc tac agc gca Ser Pro Val Thr Ser Ala Gln Gly Thr Tyr Arg Cys Tyr Ser Ala 385 390 395	1260
atc agg tcc tac ccc tac ctg ctg tcc agc cct agt tac ccc cag gag Ile Arg Ser Tyr Pro Tyr Leu Leu Ser Ser Pro Ser Tyr Pro Gln Glu 400 405 410	1308
ctc gtg gtc tca gga ccc tct ggg gat ccc agc ctc tca cct aca ggc Leu Val Val Ser Gly Pro Ser Gly Asp Pro Ser Leu Ser Pro Thr Gly 415 420 425 430	1356
tcc acc ccc aca cct ggc cct gag gac cag ccc ctc acc ccc acg ggg Ser Thr Pro Thr Pro Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly 435 440 445	1404
ttg gat ccc cag agt ggt ctg gga agg cac ctg ggg gtt gtg act ggg Leu Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val Val Thr Gly 450 455 460	1452
gtc tca gtg gcc ttc gtc ctg ctg ctg ttc ctc ctc ctc ttc ctc ctc Val Ser Val Ala Phe Val Leu Leu Leu Phe Leu Leu Leu Phe Leu Leu 465 470 475	1500
ctc cga cat cgg cat cag agc aaa cac agg aca tcg gcc cat ttc tac Leu Arg His Arg His Gln Ser Lys His Arg Thr Ser Ala His Phe Tyr 480 485 490	1548
cgt cct gca ggg gct gcg ggg cca gag ccc aag gac cag ggc ctg cag Arg Pro Ala Gly Ala Ala Gly Pro Glu Pro Lys Asp Gln Gly Leu Gln 495 500 505 510	1596
aag agg gcc agc cca gtt gct gac atc cag gag gaa att ctc aat gct Lys Arg Ala Ser Pro Val Ala Asp Ile Gln Glu Glu Ile Leu Asn Ala 515 520 525	1644
gcc gtg aag gac aca cag ccc aag gac ggg gtg gag atg gat gct cgg Ala Val Lys Asp Thr Gln Pro Lys Asp Gly Val Glu Met Asp Ala Arg 530 535 540	1692
gct gct gca tct gaa gcc ccc cag gat gtg acc tac gcc cag ctg cac Ala Ala Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His 545 550 555	1740
agc ttg acc ctc aga cgg gag gca act gag cct cct cca tcc cag gaa Ser Leu Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu 560 565 570	1788
agg gaa cct cca gct gaa ccc agc atc tac gcc ccc ctg gcc atc cac Arg Glu Pro Pro Ala Glu Pro Ser Ile Tyr Ala Pro Leu Ala Ile His 575 580 585 590	1836
tag cccacggggg acccagatct cataactcaac agaaggagac tcagagactc	1889
cagaaggcacc aggagctgcc cccagtggac accaatgaac cccagccagc ctggaccct	1949
aacaaagacc accaggacat cctgggaact ctgggactca ctagattctg cagtcaaga	2009
tgactaatat ccttgcatTT ttgaaatgaa gccacagact tctcaataaa tc	2061

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<210> SEQ ID NO 22
<211> LENGTH: 590
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Met Thr Leu Thr Leu Ser Val Leu Ile Cys Leu Gly Leu Ser Val Gly
1          5          10          15

Pro Arg Thr Cys Val Gln Ala Gly Thr Leu Pro Lys Pro Thr Leu Trp
20          25          30

Ala Glu Pro Ala Ser Val Ile Ala Arg Gly Lys Pro Val Thr Leu Trp
35          40          45

Cys Gln Gly Pro Leu Glu Thr Glu Glu Tyr Arg Leu Asp Lys Glu Gly
50          55          60

Leu Pro Trp Ala Arg Lys Arg Gln Asn Pro Leu Glu Pro Gly Ala Lys
65          70          75          80

Ala Lys Phe His Ile Pro Ser Thr Val Tyr Asp Ser Ala Gly Arg Tyr
85          90          95

Arg Cys Tyr Tyr Glu Thr Pro Ala Gly Trp Ser Glu Pro Ser Asp Pro
100         105         110

Leu Glu Leu Val Ala Thr Gly Phe Tyr Ala Glu Pro Thr Leu Leu Ala
115         120         125

Leu Pro Ser Pro Val Val Ala Ser Gly Gly Asn Val Thr Leu Gln Cys
130         135         140

Asp Thr Leu Asp Gly Leu Leu Thr Phe Val Leu Val Glu Glu Glu Gln
145         150         155         160

Lys Leu Pro Arg Thr Leu Tyr Ser Gln Lys Leu Pro Lys Gly Pro Ser
165         170         175

Gln Ala Leu Phe Pro Val Gly Pro Val Thr Pro Ser Cys Arg Trp Arg
180         185         190

Phe Arg Cys Tyr Tyr Tyr Arg Lys Asn Pro Gln Val Trp Ser Asn
195         200         205

Pro Ser Asp Leu Leu Glu Ile Leu Val Pro Gly Val Ser Arg Lys Pro
210         215         220

Ser Leu Leu Ile Pro Gln Gly Ser Val Val Ala Arg Gly Gly Ser Leu
225         230         235         240

Thr Leu Gln Cys Arg Ser Asp Val Gly Tyr Asp Ile Phe Val Leu Tyr
245         250         255

Lys Glu Gly Glu His Asp Leu Val Gln Gly Ser Gly Gln Gln Pro Gln
260         265         270

Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser Arg Ser
275         280         285

His Gly Gly Gln Tyr Arg Cys Tyr Gly Ala His Asn Leu Ser Pro Arg
290         295         300

Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Ala Gly Leu Ile
305         310         315         320

Pro Asp Ile Pro Ala Leu Ser Val Gln Pro Gly Pro Lys Val Ala Ser
325         330         335

Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Trp His Gln Ile Asp Thr
340         345         350

Phe Phe Leu Thr Lys Glu Gly Ala Ala His Pro Pro Leu Cys Leu Lys
355         360         365

Ser Lys Tyr Gln Ser Tyr Arg His Gln Ala Glu Phe Ser Met Ser Pro
370         375         380

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Val Thr Ser Ala Gln Gly Gly Thr Tyr Arg Cys Tyr Ser Ala Ile Arg
 385 390 395 400
 Ser Tyr Pro Tyr Leu Leu Ser Ser Pro Ser Tyr Pro Gln Glu Leu Val
 405 410 415
 Val Ser Gly Pro Ser Gly Asp Pro Ser Leu Ser Pro Thr Gly Ser Thr
 420 425 430
 Pro Thr Pro Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly Leu Asp
 435 440 445
 Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val Val Thr Gly Val Ser
 450 455 460
 Val Ala Phe Val Leu Leu Leu Phe Leu Leu Leu Phe Leu Leu Leu Arg
 465 470 475 480
 His Arg His Gln Ser Lys His Arg Thr Ser Ala His Phe Tyr Arg Pro
 485 490 495
 Ala Gly Ala Ala Gly Pro Glu Pro Lys Asp Gln Gly Leu Gln Lys Arg
 500 505 510
 Ala Ser Pro Val Ala Asp Ile Gln Glu Glu Ile Leu Asn Ala Ala Val
 515 520 525
 Lys Asp Thr Gln Pro Lys Asp Gly Val Glu Met Asp Ala Arg Ala Ala
 530 535 540
 Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu
 545 550 555 560
 Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Ser Gln Glu Arg Glu
 565 570 575
 Pro Pro Ala Glu Pro Ser Ile Tyr Ala Pro Leu Ala Ile His
 580 585 590

<210> SEQ ID NO 23

<211> LENGTH: 28

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

tatgcgccg ccatgatgac aatgtggt

28

<210> SEQ ID NO 24

<211> LENGTH: 25

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

tatgcgccg ccccttgca tagcg

25

<210> SEQ ID NO 25

<211> LENGTH: 31

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

atagtcgaca acgcatcat gagatgtggt g

31

<210> SEQ ID NO 26

<211> LENGTH: 29

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

taaagatctg ggctcgtag ctgtcgggt

29

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<210> SEQ ID NO 27
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

tatagatcta cccccaggtg ccttcccaga cca

33

<210> SEQ ID NO 28
 <211> LENGTH: 111
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: MISC_FEATURE
 <222> LOCATION: (2)..(2)
 <223> OTHER INFORMATION: Xaa is Gly or Arg
 <220> FEATURE:
 <221> NAME/KEY: MISC_FEATURE
 <222> LOCATION: (5)..(5)
 <223> OTHER INFORMATION: Xaa is Leu or Val
 <220> FEATURE:
 <221> NAME/KEY: MISC_FEATURE
 <222> LOCATION: (6)..(6)
 <223> OTHER INFORMATION: Xaa is Gly or Asp
 <220> FEATURE:
 <221> NAME/KEY: MISC_FEATURE
 <222> LOCATION: (10)..(10)
 <223> OTHER INFORMATION: Xaa is His, Arg or Cys
 <220> FEATURE:
 <221> NAME/KEY: MISC_FEATURE
 <222> LOCATION: (11)..(11)
 <223> OTHER INFORMATION: Xaa is Val or Met
 <220> FEATURE:
 <221> NAME/KEY: MISC_FEATURE
 <222> LOCATION: (13)..(13)
 <223> OTHER INFORMATION: Xaa is Ala or Thr
 <220> FEATURE:
 <221> NAME/KEY: MISC_FEATURE
 <222> LOCATION: (15)..(15)
 <223> OTHER INFORMATION: Xaa is His, Pro or Thr
 <220> FEATURE:
 <221> NAME/KEY: MISC_FEATURE
 <222> LOCATION: (16)..(16)
 <223> OTHER INFORMATION: Xaa is Leu, Ile or Phe
 <220> FEATURE:
 <221> NAME/KEY: MISC_FEATURE
 <222> LOCATION: (18)..(18)
 <223> OTHER INFORMATION: Xaa is Gly, Asp or Ala
 <220> FEATURE:
 <221> NAME/KEY: MISC_FEATURE
 <222> LOCATION: (26)..(26)
 <223> OTHER INFORMATION: Xaa is Thr, Ile, Ser or Ala
 <220> FEATURE:
 <221> NAME/KEY: MISC_FEATURE
 <222> LOCATION: (30)..(30)
 <223> OTHER INFORMATION: Xaa is Thr, Ile, Ser or Ala
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (31)..(100)
 <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
 <220> FEATURE:
 <221> NAME/KEY: MISC_FEATURE
 <222> LOCATION: (106)..(106)
 <223> OTHER INFORMATION: Xaa is Gly or Val
 <220> FEATURE:
 <221> NAME/KEY: MISC_FEATURE
 <222> LOCATION: (109)..(109)
 <223> OTHER INFORMATION: Xaa is Met or Ala

<400> SEQUENCE: 28

Leu Xaa Leu Ser Xaa Xaa Pro Arg Thr Xaa Xaa Gln Xaa Gly Xaa Xaa
 1 5 10 15

Pro Xaa Pro Thr Leu Trp Ala Glu Pro Xaa Ser Phe Ile Xaa Xaa Xaa

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	20	25	30	
Xaa	35	40	45	
Xaa	50	55	60	
Xaa	65	70	75	80
Xaa	85	90	95	
Xaa Xaa Xaa Xaa Ser Asp Pro Lys Leu Xaa Leu Val Xaa Thr Gly	100	105	110	
<p><210> SEQ ID NO 29 <211> LENGTH: 1016 <212> TYPE: DNA <213> ORGANISM: Homo sapiens <220> FEATURE: <221> NAME/KEY: CDS <222> LOCATION: (69)..(968)</p>				
<p><400> SEQUENCE: 29</p>				
ctgagtctgc ctgtggcatg gacctgcac ttcctgaag catctccagg gctgaaaaat				60
cactgacc atg gca cca tgg tct cat cca tct gca cag ctg cag cca gtg				110
Met Ala Pro Trp Ser His Pro Ser Ala Gln Leu Gln Pro Val	1	5	10	
gga gga gac gcc gtg agc cct gcc ctg atg gtt ctg ctg tgc ctg ggg				158
Gly Gly Asp Ala Val Ser Pro Ala Leu Met Val Leu Leu Cys Leu Gly	15	20	25	30
ctg agt ctg ggc ccc agg acc cac gtg cag gca ggg aac ctg tcc aaa				206
Leu Ser Leu Gly Pro Arg Thr His Val Gln Ala Gly Asn Leu Ser Lys	35	40	45	
gcc acc ctg tgg gct gag cca ggc tct gtg atc agc cgg ggg aac tct				254
Ala Thr Leu Trp Ala Glu Pro Gly Ser Val Ile Ser Arg Gly Asn Ser	50	55	60	
gtg acc atc cgg tgt cag ggg acc ctg gag gcc cag gaa tac cgt ctg				302
Val Thr Ile Arg Cys Gln Gly Thr Leu Glu Ala Gln Glu Tyr Arg Leu	65	70	75	
gtt aaa gag gga agc cca gaa ccc tgg gac aca cag aac cca ctg gag				350
Val Lys Glu Gly Ser Pro Glu Pro Trp Asp Thr Gln Asn Pro Leu Glu	80	85	90	
ccc aag aac aag gcc aga ttc tcc atc cca tcc atg aca gag cac cat				398
Pro Lys Asn Lys Ala Arg Phe Ser Ile Pro Ser Met Thr Glu His His	95	100	105	110
gca ggg aga tac cgc tgt tac tac tac agc cct gca ggc tgg tca gag				446
Ala Gly Arg Tyr Arg Cys Tyr Tyr Tyr Ser Pro Ala Gly Trp Ser Glu	115	120	125	
ccc agc gac ccc ctg gag ctg gtg gtg aca gga ttc tac aac aaa ccc				494
Pro Ser Asp Pro Leu Glu Leu Val Val Thr Gly Phe Tyr Asn Lys Pro	130	135	140	
acc ctg tca gcc ctg ccc agt cct gtg gtg acc tca gga gag aac gtg				542
Thr Leu Ser Ala Leu Pro Ser Pro Val Val Thr Ser Gly Glu Asn Val	145	150	155	
acc ctg cag tgt ggc tca cgg ctg aga ttc gac agg ttc att ctg act				590
Thr Leu Gln Cys Gly Ser Arg Leu Arg Phe Asp Arg Phe Ile Leu Thr	160	165	170	
gag gaa gga gac cac aag ctg tcc tgg acc ttg gac tca cag ctg acc				638
Glu Glu Gly Asp His Lys Leu Ser Trp Thr Leu Asp Ser Gln Leu Thr	175	180	185	190
ccc agt ggg cag ttc cag gcc ctg ttc cct gtg ggc cct gtg acc ccc				686

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Pro Ser Gly Gln Phe Gln Ala Leu Phe Pro Val Gly Pro Val Thr Pro
      195                200                205

agc cac agg tgg atg ctc aga tgc tat ggc tct cgc agg cat atc ctg      734
Ser His Arg Trp Met Leu Arg Cys Tyr Gly Ser Arg Arg His Ile Leu
      210                215                220

cag gta tgg tca gaa ccc agt gac ctc ctg gag att ccg gtc tca gga      782
Gln Val Trp Ser Glu Pro Ser Asp Leu Leu Glu Ile Pro Val Ser Gly
      225                230                235

gca gct gat aac ctc agt ccg tca caa aac aag tct gac tct ggg act      830
Ala Ala Asp Asn Leu Ser Pro Ser Gln Asn Lys Ser Asp Ser Gly Thr
      240                245                250

gcc tca cac ctt cag gat tac gca gta gag aat ctc atc cgc atg ggc      878
Ala Ser His Leu Gln Asp Tyr Ala Val Glu Asn Leu Ile Arg Met Gly
      255                260                265                270

atg gcc ggc ttg atc ctg gtg gtc ctt ggg att ctg ata ttt cag gat      926
Met Ala Gly Leu Ile Leu Val Val Leu Gly Ile Leu Ile Phe Gln Asp
      275                280                285

tgg cac agc cag aga agc ccc caa gct gca gct gga agg tga      968
Trp His Ser Gln Arg Ser Pro Gln Ala Ala Ala Gly Arg
      290                295

acagaagaga gaacaatgca ccattgaatg ctggagcctt ggaagcga      1016

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<210> SEQ ID NO 30
<211> LENGTH: 299
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 30

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Met Ala Pro Trp Ser His Pro Ser Ala Gln Leu Gln Pro Val Gly Gly
 1      5      10      15

Asp Ala Val Ser Pro Ala Leu Met Val Leu Leu Cys Leu Gly Leu Ser
 20     25     30

Leu Gly Pro Arg Thr His Val Gln Ala Gly Asn Leu Ser Lys Ala Thr
 35     40     45

Leu Trp Ala Glu Pro Gly Ser Val Ile Ser Arg Gly Asn Ser Val Thr
 50     55     60

Ile Arg Cys Gln Gly Thr Leu Glu Ala Gln Glu Tyr Arg Leu Val Lys
 65     70     75     80

Glu Gly Ser Pro Glu Pro Trp Asp Thr Gln Asn Pro Leu Glu Pro Lys
 85     90     95

Asn Lys Ala Arg Phe Ser Ile Pro Ser Met Thr Glu His His Ala Gly
100    105    110

Arg Tyr Arg Cys Tyr Tyr Tyr Ser Pro Ala Gly Trp Ser Glu Pro Ser
115    120    125

Asp Pro Leu Glu Leu Val Val Thr Gly Phe Tyr Asn Lys Pro Thr Leu
130    135    140

Ser Ala Leu Pro Ser Pro Val Val Thr Ser Gly Glu Asn Val Thr Leu
145    150    155    160

Gln Cys Gly Ser Arg Leu Arg Phe Asp Arg Phe Ile Leu Thr Glu Glu
165    170    175

Gly Asp His Lys Leu Ser Trp Thr Leu Asp Ser Gln Leu Thr Pro Ser
180    185    190

Gly Gln Phe Gln Ala Leu Phe Pro Val Gly Pro Val Thr Pro Ser His
195    200    205

Arg Trp Met Leu Arg Cys Tyr Gly Ser Arg Arg His Ile Leu Gln Val
210    215    220

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Trp	Ser	Glu	Pro	Ser	Asp	Leu	Leu	Glu	Ile	Pro	Val	Ser	Gly	Ala	Ala
225					230					235					240
Asp	Asn	Leu	Ser	Pro	Ser	Gln	Asn	Lys	Ser	Asp	Ser	Gly	Thr	Ala	Ser
				245					250					255	
His	Leu	Gln	Asp	Tyr	Ala	Val	Glu	Asn	Leu	Ile	Arg	Met	Gly	Met	Ala
			260					265					270		
Gly	Leu	Ile	Leu	Val	Val	Leu	Gly	Ile	Leu	Ile	Phe	Gln	Asp	Trp	His
		275					280					285			
Ser	Gln	Arg	Ser	Pro	Gln	Ala	Ala	Ala	Gly	Arg					
	290					295									

<210> SEQ ID NO 31

<211> LENGTH: 1007

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (95)..(958)

<400> SEQUENCE: 31

caggtgtcag atgtgtctct gctgatctga gtctgcctgt ggcattggacc tgcattctcc	60
ctgaagcatc tccagggtcg aaaaatcact gacc atg gca cca tgg tct cat cca	115
Met Ala Pro Trp Ser His Pro	
1 5	
tct gca cag ctg cag cca gtg gga gga gac gcc gtg agc cct gcc ctc	163
Ser Ala Gln Leu Gln Pro Val Gly Gly Asp Ala Val Ser Pro Ala Leu	
10 15 20	
atg gtt ctg ctc tgc ctc ggg aac ctc tcc aaa gcc acc ctc tgg gct	211
Met Val Leu Leu Cys Leu Gly Asn Leu Ser Lys Ala Thr Leu Trp Ala	
25 30 35	
gag cca ggc tct gtg atc agc cgg ggg aac tct gtg acc atc cgg tgt	259
Glu Pro Gly Ser Val Ile Ser Arg Gly Asn Ser Val Thr Ile Arg Cys	
40 45 50 55	
cag ggg acc ctg gag gcc cag gaa tac cgt ctg gtt aaa gag gga agc	307
Gln Gly Thr Leu Glu Ala Gln Glu Tyr Arg Leu Val Lys Glu Gly Ser	
60 65 70	
cca gaa ccc tgg gac aca cag aac cca ctg gag ccc aag aac aag gcc	355
Pro Glu Pro Trp Asp Thr Gln Asn Pro Leu Glu Pro Lys Asn Lys Ala	
75 80 85	
aga ttc tcc atc cca tcc atg aca gag cac cat gca ggg aga tac cgc	403
Arg Phe Ser Ile Pro Ser Met Thr Glu His His Ala Gly Arg Tyr Arg	
90 95 100	
tgt tac tac tac agc cct gca ggc tgg tca gag ccc agc gac ccc ctg	451
Cys Tyr Tyr Tyr Ser Pro Ala Gly Trp Ser Glu Pro Ser Asp Pro Leu	
105 110 115	
gag ctg gtg gtg aca gga ttc tac aac aaa ccc acc ctc tca gcc ctg	499
Glu Leu Val Val Thr Gly Phe Tyr Asn Lys Pro Thr Leu Ser Ala Leu	
120 125 130 135	
ccc agt cct gtg gtg acc tca gga gag aac gtg acc ctc cag tgt ggc	547
Pro Ser Pro Val Thr Ser Gly Glu Asn Val Thr Leu Gln Cys Gly	
140 145 150	
tca cgg ctg aga ttc gac agg ttc att ctg act gag gaa gga gac cac	595
Ser Arg Leu Arg Phe Asp Arg Phe Ile Leu Thr Glu Glu Gly Asp His	
155 160 165	
aag ctc tcc tgg acc ttg gac tca cag ctg acc ccc agt ggg cag ttc	643
Lys Leu Ser Trp Thr Leu Asp Ser Gln Leu Thr Pro Ser Gly Gln Phe	
170 175 180	
cag gcc ctg ttc cct gtg ggc cct gtg acc ccc agc cac agg tgg atg	691
Gln Ala Leu Phe Pro Val Gly Pro Val Thr Pro Ser His Arg Trp Met	
185 190 195	

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Gly Thr Ala Ser His Leu Gln Asp Tyr Ala Val Glu Asn Leu Ile Arg
245 250 255

Met Gly Met Ala Gly Leu Ile Leu Val Val Leu Gly Ile Leu Ile Phe
260 265 270

Gln Asp Trp His Ser Gln Arg Ser Pro Gln Ala Ala Ala Gly Arg
275 280 285

<210> SEQ ID NO 33
<211> LENGTH: 956
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (115)..(912)

<400> SEQUENCE: 33

ctcagcctgg gctacacagc caggtgtcag atgtgtctct gctgatctga gctgcctgt 60

ggcatggacc tgcattctcc ctgaagcatc tccagggctg aaaaatcact gacc atg 117
Met
1

gca cca tgg tct cat cca tct gca cag ctg cag cca gtg gga gga gac 165
Ala Pro Trp Ser His Pro Ser Ala Gln Leu Gln Pro Val Gly Gly Asp
5 10 15

gcc gtg agc cct gcc ctc atg gtt ctg ctc tgc ctc ggg ctg agt ctg 213
Ala Val Ser Pro Ala Leu Met Val Leu Leu Cys Leu Gly Leu Ser Leu
20 25 30

ggc ccc agg acc cac gtg cag gca ggg aac ctc tcc aaa gcc acc ctc 261
Gly Pro Arg Thr His Val Gln Ala Gly Asn Leu Ser Lys Ala Thr Leu
35 40 45

tgg gct gag cca ggc tct gtg atc agc cgg ggg aac tct gtg acc atc 309
Trp Ala Glu Pro Gly Ser Val Ile Ser Arg Gly Asn Ser Val Thr Ile
50 55 60 65

cgg tgt cag ggg acc ctg gag gcc cag gaa tac cgt ctg gtt aaa gag 357
Arg Cys Gln Gly Thr Leu Glu Ala Gln Glu Tyr Arg Leu Val Lys Glu
70 75 80

gga agc cca gaa ccc tgg gac aca cag aac cca ctg gag ccc aag aac 405
Gly Ser Pro Glu Pro Trp Asp Thr Gln Asn Pro Leu Glu Pro Lys Asn
85 90 95

aag gcc aga ttc tcc atc cca tcc atg aca gag cac cat gca ggg aga 453
Lys Ala Arg Phe Ser Ile Pro Ser Met Thr Glu His His Ala Gly Arg
100 105 110

tac cgc tgt tac tac tac agc cct gca ggc tgg tca gag ccc agc gac 501
Tyr Arg Cys Tyr Tyr Tyr Ser Pro Ala Gly Trp Ser Glu Pro Ser Asp
115 120 125

ccc ctg gag ctg gtg gtg aca gga ttc tac aac aaa ccc acc ctc tca 549
Pro Leu Glu Leu Val Val Thr Gly Phe Tyr Asn Lys Pro Thr Leu Ser
130 135 140 145

gcc ctg ccc agt cct gtg gtg acc tca gga gag aac gtg acc ctc cag 597
Ala Leu Pro Ser Pro Val Val Thr Ser Gly Glu Asn Val Thr Leu Gln
150 155 160

tgt ggc tca cgg ctg aga ttc gac agg ttc att ctg act gag gaa gga 645
Cys Gly Ser Arg Leu Arg Phe Asp Arg Phe Ile Leu Thr Glu Glu Gly
165 170 175

gac cac aag ctc tcc tgg acc ttg gac tca cag ctg acc ccc agt ggg 693
Asp His Lys Leu Ser Trp Thr Leu Asp Ser Gln Leu Thr Pro Ser Gly
180 185 190

cag ttc cag gcc ctg ttc cct gtg ggc cct gtg acc ccc agc cac agg 741
Gln Phe Gln Ala Leu Phe Pro Val Gly Pro Val Thr Pro Ser His Arg
195 200 205

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tgg atg ctc aga tgc tat ggc tct cgc agg cat atc ctg cag gta tgg	789
Trp Met Leu Arg Cys Tyr Gly Ser Arg Arg His Ile Leu Gln Val Trp	
210 215 220 225	
tca gaa ccc agt gac ctc ctg gag att ccg gtc tca ggt gag gaa gcc	837
Ser Glu Pro Ser Asp Leu Leu Glu Ile Pro Val Ser Gly Glu Glu Ala	
230 235 240	
aca gtc ttc tct agt aca att cag gga agc cag aca ggt tgt gga gag	885
Thr Val Phe Ser Ser Thr Ile Gln Gly Ser Gln Thr Gly Cys Gly Glu	
245 250 255	
ctt tac agg cag ggc agc ccc tgc taa gaaagacaaa aaggggaagg	932
Leu Tyr Arg Gln Gly Ser Pro Cys	
260 265	
agaacacaga aatcctaggg acac	956

<210> SEQ ID NO 34
 <211> LENGTH: 265
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Met Ala Pro Trp Ser His Pro Ser Ala Gln Leu Gln Pro Val Gly Gly	
1 5 10 15	
Asp Ala Val Ser Pro Ala Leu Met Val Leu Leu Cys Leu Gly Leu Ser	
20 25 30	
Leu Gly Pro Arg Thr His Val Gln Ala Gly Asn Leu Ser Lys Ala Thr	
35 40 45	
Leu Trp Ala Glu Pro Gly Ser Val Ile Ser Arg Gly Asn Ser Val Thr	
50 55 60	
Ile Arg Cys Gln Gly Thr Leu Glu Ala Gln Glu Tyr Arg Leu Val Lys	
65 70 75 80	
Glu Gly Ser Pro Glu Pro Trp Asp Thr Gln Asn Pro Leu Glu Pro Lys	
85 90 95	
Asn Lys Ala Arg Phe Ser Ile Pro Ser Met Thr Glu His His Ala Gly	
100 105 110	
Arg Tyr Arg Cys Tyr Tyr Tyr Ser Pro Ala Gly Trp Ser Glu Pro Ser	
115 120 125	
Asp Pro Leu Glu Leu Val Val Thr Gly Phe Tyr Asn Lys Pro Thr Leu	
130 135 140	
Ser Ala Leu Pro Ser Pro Val Val Thr Ser Gly Glu Asn Val Thr Leu	
145 150 155 160	
Gln Cys Gly Ser Arg Leu Arg Phe Asp Arg Phe Ile Leu Thr Glu Glu	
165 170 175	
Gly Asp His Lys Leu Ser Trp Thr Leu Asp Ser Gln Leu Thr Pro Ser	
180 185 190	
Gly Gln Phe Gln Ala Leu Phe Pro Val Gly Pro Val Thr Pro Ser His	
195 200 205	
Arg Trp Met Leu Arg Cys Tyr Gly Ser Arg Arg His Ile Leu Gln Val	
210 215 220	
Trp Ser Glu Pro Ser Asp Leu Leu Glu Ile Pro Val Ser Gly Glu Glu	
225 230 235 240	
Ala Thr Val Phe Ser Ser Thr Ile Gln Gly Ser Gln Thr Gly Cys Gly	
245 250 255	
Glu Leu Tyr Arg Gln Gly Ser Pro Cys	
260 265	

<210> SEQ ID NO 35

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<211> LENGTH: 997
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (73)..(834)

<400> SEQUENCE: 35

tgatctgagt ctgcctgtgg catggacctg catcttcctt gaagcatctc cagggtgaa      60

aaatcactga cc atg gca cca tgg tct cat cca tct gca cag ctg cag cca      111
      Met Ala Pro Trp Ser His Pro Ser Ala Gln Leu Gln Pro
      1          5          10

gtg gga gga gac gcc gtg agc cct gcc ctg atg gtt ctg ctg tgc ctg      159
Val Gly Gly Asp Ala Val Ser Pro Ala Leu Met Val Leu Leu Cys Leu
      15          20          25

ggg aac ctg tcc aaa gcc acc ctg tgg gct gag cca ggc tct gtg atc      207
Gly Asn Leu Ser Lys Ala Thr Leu Trp Ala Glu Pro Gly Ser Val Ile
      30          35          40          45

agc cgg ggg aac tct gtg acc atc cgg tgt cag ggg acc ctg gag gcc      255
Ser Arg Gly Asn Ser Val Thr Ile Arg Cys Gln Gly Thr Leu Glu Ala
      50          55          60

cag gaa tac cgt ctg gtt aaa gag gga agc cca gaa ccc tgg gac aca      303
Gln Glu Tyr Arg Leu Val Lys Glu Gly Ser Pro Glu Pro Trp Asp Thr
      65          70          75

cag aac cca ctg gag ccc aag aac aag gcc aga ttc tcc atc cca tcc      351
Gln Asn Pro Leu Glu Pro Lys Asn Lys Ala Arg Phe Ser Ile Pro Ser
      80          85          90

atg aca gag cac cat gca ggg aga tac cgc tgt tac tac tac agc cct      399
Met Thr Glu His His Ala Gly Arg Tyr Arg Cys Tyr Tyr Tyr Ser Pro
      95          100          105

gca ggc tgg tca gag ccc agc gac ccc ctg gag ctg gtg gtg aca gga      447
Ala Gly Trp Ser Glu Pro Ser Asp Pro Leu Glu Leu Val Val Thr Gly
      110          115          120          125

ttc tac aac aaa ccc acc ctg tca gcc ctg ccc agt cct gtg gtg acc      495
Phe Tyr Asn Lys Pro Thr Leu Ser Ala Leu Pro Ser Pro Val Val Thr
      130          135          140

tca gga gag aac gtg acc ctg cag tgt ggc tca cgg ctg aga ttc gac      543
Ser Gly Glu Asn Val Thr Leu Gln Cys Gly Ser Arg Leu Arg Phe Asp
      145          150          155

agg ttc att ctg act gag gaa gga gac cac aag ctg tcc tgg acc ttg      591
Arg Phe Ile Leu Thr Glu Glu Gly Asp His Lys Leu Ser Trp Thr Leu
      160          165          170

gac tca cag ctg acc ccc agt ggg cag ttc cag gcc ctg ttc cct gtg      639
Asp Ser Gln Leu Thr Pro Ser Gly Gln Phe Gln Ala Leu Phe Pro Val
      175          180          185

ggc cct gtg acc ccc agc cac agg tgg atg ctg aga tgc tat ggc tct      687
Gly Pro Val Thr Pro Ser His Arg Trp Met Leu Arg Cys Tyr Gly Ser
      190          195          200          205

cgc agg cat atc ctg cag gta tgg tca gaa ccc agt gac ctg ctg gag      735
Arg Arg His Ile Leu Gln Val Trp Ser Glu Pro Ser Asp Leu Leu Glu
      210          215          220

att ccg gtc tca ggt gag gaa gcc aca gtc ttc tct agt aca att cag      783
Ile Pro Val Ser Gly Glu Glu Ala Thr Val Phe Ser Ser Thr Ile Gln
      225          230          235

gga agc cag aca ggt tgt gga gag ctt tac agg cag ggc agc ccc tgc      831
Gly Ser Gln Thr Gly Cys Gly Glu Leu Tyr Arg Gln Gly Ser Pro Cys
      240          245          250

taa gaaagacaaa aagggaagg agaacacaga aatcctaggg acacaaattc      884

agggtgagga aaacaaagca agggctgggc acagtggctc acacgtgtaa tctcagcact      944

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 ttgggagggc gaggcaggtg gatcacctga tgtcaggagt tcaagaccag cct 997

<210> SEQ ID NO 36
 <211> LENGTH: 253
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Met Ala Pro Trp Ser His Pro Ser Ala Gln Leu Gln Pro Val Gly Gly
 1 5 10 15
 Asp Ala Val Ser Pro Ala Leu Met Val Leu Leu Cys Leu Gly Asn Leu
 20 25 30
 Ser Lys Ala Thr Leu Trp Ala Glu Pro Gly Ser Val Ile Ser Arg Gly
 35 40 45
 Asn Ser Val Thr Ile Arg Cys Gln Gly Thr Leu Glu Ala Gln Glu Tyr
 50 55 60
 Arg Leu Val Lys Glu Gly Ser Pro Glu Pro Trp Asp Thr Gln Asn Pro
 65 70 75 80
 Leu Glu Pro Lys Asn Lys Ala Arg Phe Ser Ile Pro Ser Met Thr Glu
 85 90 95
 His His Ala Gly Arg Tyr Arg Cys Tyr Tyr Tyr Ser Pro Ala Gly Trp
 100 105 110
 Ser Glu Pro Ser Asp Pro Leu Glu Leu Val Val Thr Gly Phe Tyr Asn
 115 120 125
 Lys Pro Thr Leu Ser Ala Leu Pro Ser Pro Val Val Thr Ser Gly Glu
 130 135 140
 Asn Val Thr Leu Gln Cys Gly Ser Arg Leu Arg Phe Asp Arg Phe Ile
 145 150 155 160
 Leu Thr Glu Glu Gly Asp His Lys Leu Ser Trp Thr Leu Asp Ser Gln
 165 170 175
 Leu Thr Pro Ser Gly Gln Phe Gln Ala Leu Phe Pro Val Gly Pro Val
 180 185 190
 Thr Pro Ser His Arg Trp Met Leu Arg Cys Tyr Gly Ser Arg Arg His
 195 200 205
 Ile Leu Gln Val Trp Ser Glu Pro Ser Asp Leu Leu Glu Ile Pro Val
 210 215 220
 Ser Gly Glu Glu Ala Thr Val Phe Ser Ser Thr Ile Gln Gly Ser Gln
 225 230 235 240
 Thr Gly Cys Gly Glu Leu Tyr Arg Gln Gly Ser Pro Cys
 245 250

<210> SEQ ID NO 37
 <211> LENGTH: 1451
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (1)..(1347)

<400> SEQUENCE: 37

ccc aag ccc acc ctc tgg gct aag cca ggc tct gtg atc agc tgg aga 48
 Pro Lys Pro Thr Leu Trp Ala Lys Pro Gly Ser Val Ile Ser Trp Arg
 1 5 10 15
 agc ccc atg acc atg tgg tgt cag ggg acc ctg gaa gcc cag gag tac 96
 Ser Pro Met Thr Met Trp Cys Gln Gly Thr Leu Glu Ala Gln Glu Tyr
 20 25 30
 cat ctg tat aaa gag gga agc aca gag ccc tgg gac aga acg aat cca 144
 His Leu Tyr Lys Glu Gly Ser Thr Glu Pro Trp Asp Arg Thr Asn Pro

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35			40			45			
ctg gag acc	agg aac aag	gcc aga tac	tcc atc cca	tcc atg aca	cag	192			
Leu Glu Thr	Arg Asn Lys	Ala Arg Tyr	Ser Ile Pro	Ser Met Thr	Gln				
50		55	60						
cac cat gca	gtg aga tat	cag tgt tac	tat ctc agc	cct gca ggc	tgg	240			
His His Ala	Val Arg Tyr	Gln Cys Tyr	Tyr Tyr Leu	Ser Pro Ala	Gly Trp				
65	70		75		80				
tca gag ccc	agt gac ccc	ctg gag ctg	gtg atg aca	gga ttc tac	agc	288			
Ser Glu Pro	Ser Asp Pro	Leu Glu Leu	Val Met Thr	Gly Phe Tyr	Ser				
	85		90		95				
aaa ccc acc	ctc tca gcc	ctg ccc agc	cct gtg gtg	gcc tca ggg	ggg	336			
Lys Pro Thr	Leu Ser Ala	Leu Pro Ser	Pro Val Val	Ala Ser Gly	Gly				
	100		105		110				
aaa gtg acc	ctc cga tgt	ggc tca cag	aag gga tat	cac cat ttt	gtt	384			
Lys Val Thr	Leu Arg Cys	Gly Ser Gln	Lys Gly Tyr	His His Phe	Val				
	115		120		125				
ctg atg aag	gaa gga gaa	cac cag ctc	ccc cgg acc	ctg gac tca	cag	432			
Leu Met Lys	Glu Gly Glu	His Gln Leu	Pro Arg Thr	Leu Asp Ser	Gln				
130		135		140					
cag ctc cac	agt ggg ggg	ttc cag gcc	ctg ttc cct	gtg ggc ccc	gtg	480			
Gln Leu His	Ser Gly Gly	Phe Gln Ala	Leu Phe Pro	Val Gly Pro	Val				
145		150		155	160				
acc ccc agc	cac agg tgg	agg ttc aca	tgc tat tac	tat tat atg	aac	528			
Thr Pro Ser	His Arg Trp	Arg Phe Thr	Cys Tyr Tyr	Tyr Tyr Met	Asn				
	165		170		175				
acc ccc cag	gtg tgg tcc	cac ccc agt	gac ccc ctg	gag att ctg	ccc	576			
Thr Pro Gln	Val Trp Ser	His Pro Ser	Asp Pro Leu	Glu Ile Leu	Pro				
	180		185		190				
tca gga cag	agc tct ccc	cct gtc ctg	gcc cct gga	gag acc ctg	acc	624			
Ser Gly Gln	Ser Ser Pro	Pro Val Leu	Ala Pro Gly	Glu Thr Leu	Thr				
195		200		205					
ctc cag tgt	ggc tct gat	gtc ggc tac	gac aga ttc	act ctg tac	aag	672			
Leu Gln Cys	Gly Ser Asp	Val Gly Tyr	Asp Arg Phe	Thr Leu Tyr	Lys				
210		215		220					
gag ggg gaa	tgt gac ttc	ctc cag cgc	cct ggc cag	cag ccc cag	gct	720			
Glu Gly Glu	Cys Asp Phe	Leu Gln Arg	Pro Gly Gln	Gln Pro Gln	Ala				
225		230		235	240				
ggg ctc tcc	cag gcc aac	ttc acc ctg	ggc cct gtg	agg ggc tcc	cac	768			
Gly Leu Ser	Gln Ala Asn	Phe Thr Leu	Gly Pro Val	Arg Gly Ser	His				
	245		250		255				
ggg ggc cag	tac aga tgc	tcc ggt gca	cac aac ctc	tcc tcc gag	tgg	816			
Gly Gly Gln	Tyr Arg Cys	Ser Gly Ala	His Asn Leu	Ser Ser Arg	Trp				
	260		265		270				
tcg gcc ccc	agt gac ccc	ctg gac atc	ctg atc gca	gga cag atc	cct	864			
Ser Ala Pro	Ser Asp Pro	Leu Asp Ile	Leu Ile Ala	Gly Gln Ile	Pro				
	275		280		285				
ggc aga ccc	tcc ctc tcg	gtg cag ttg	tgg ccc aca	gtg gcc tca	gga	912			
Gly Arg Pro	Ser Leu Ser	Val Gln Leu	Trp Pro Thr	Val Ala Ser	Gly				
290		295		300					
gag aac gtg	acc ctg ctg	tgt caa tca	caa gag tgg	atg cac act	ttc	960			
Glu Asn Val	Thr Leu Leu	Cys Gln Ser	Gln Glu Trp	Met His Thr	Phe				
305		310		315	320				
ctt ctg acc	aag gag ggg	gca gcc cat	ccc ctg ctg	tgt ctg aga	tca	1008			
Leu Leu Thr	Lys Glu Gly	Ala Ala His	Pro Leu Leu	Cys Leu Arg	Ser				
	325		330		335				
aag tac gga	gct cat aag	tac cag gct	gaa ttc ccc	atg agt cct	gtg	1056			
Lys Tyr Gly	Ala His Lys	Tyr Gln Ala	Glu Phe Pro	Met Ser Pro	Val				
	340		345		350				
acc tca gcc	cac acg ggg	acc tac agg	tgc tac ggc	tca ctc agc	tcc	1104			

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225		230		235		240									
Gly	Leu	Ser	Gln	Ala	Asn	Phe	Thr	Leu	Gly	Pro	Val	Arg	Gly	Ser	His
				245					250					255	
Gly	Gly	Gln	Tyr	Arg	Cys	Ser	Gly	Ala	His	Asn	Leu	Ser	Ser	Glu	Trp
			260					265						270	
Ser	Ala	Pro	Ser	Asp	Pro	Leu	Asp	Ile	Leu	Ile	Ala	Gly	Gln	Ile	Pro
		275					280					285			
Gly	Arg	Pro	Ser	Leu	Ser	Val	Gln	Leu	Trp	Pro	Thr	Val	Ala	Ser	Gly
	290					295					300				
Glu	Asn	Val	Thr	Leu	Leu	Cys	Gln	Ser	Gln	Glu	Trp	Met	His	Thr	Phe
305					310					315					320
Leu	Leu	Thr	Lys	Glu	Gly	Ala	Ala	His	Pro	Leu	Leu	Cys	Leu	Arg	Ser
				325					330					335	
Lys	Tyr	Gly	Ala	His	Lys	Tyr	Gln	Ala	Glu	Phe	Pro	Met	Ser	Pro	Val
			340					345						350	
Thr	Ser	Ala	His	Thr	Gly	Thr	Tyr	Arg	Cys	Tyr	Gly	Ser	Leu	Ser	Ser
		355					360					365			
Asp	Pro	Tyr	Leu	Leu	Ser	His	Pro	Ser	Gly	Pro	Val	Glu	Leu	Val	Val
	370					375					380				
Ser	Ala	Ser	His	Leu	Gln	Asp	Tyr	Ala	Val	Glu	Asn	Leu	Ile	His	Met
385					390					395					400
Gly	Val	Ala	Gly	Leu	Ile	Leu	Val	Val	Leu	Gly	Ile	Leu	Ser	Phe	Glu
				405					410					415	
Ala	Trp	His	Ser	Gln	Arg	Ser	Phe	Pro	Arg	Cys	Ser	Arg	Glu	Val	Asn
			420					425					430		
Ser	Arg	Glu	Asp	Asn	Val	Leu	Tyr	Arg	Val	Val	Lys	Pro	Gln	Glu	Gln
		435					440					445			

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<210> SEQ ID NO 39
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

Asp Tyr Lys Asp Asp Asp Asp Lys
 1 5

What is claimed is:
 1. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:
 amino acids x_1 to 262 of SEQ ID NO:30, wherein x_1 is amino acid 1 or 35;
 amino acids x_2 to 250 of SEQ ID NO:32, wherein x_2 is amino acid 1 or 36;
 amino acids x_3 to 265 of SEQ ID NO:34, wherein x_3 is amino acid 1 or 35; and
 amino acids x_4 to 253 of SEQ ID NO:36, wherein x_4 is amino acid 1 or 36.
 2. The isolated polypeptide of claim 1, comprising an amino acid sequence selected from the group consisting of

SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, and SEQ ID NO:36.
 3. A composition comprising a physiologically acceptable carrier and a polypeptide of claim 2.
 4. The isolated polypeptide of claim 1, which further comprises an Fc region of an immunoglobulin.
 5. A composition comprising a physiologically acceptable carrier and a polypeptide of claim 4.
 6. A composition comprising a physiologically acceptable carrier and a polypeptide of claim 1.

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